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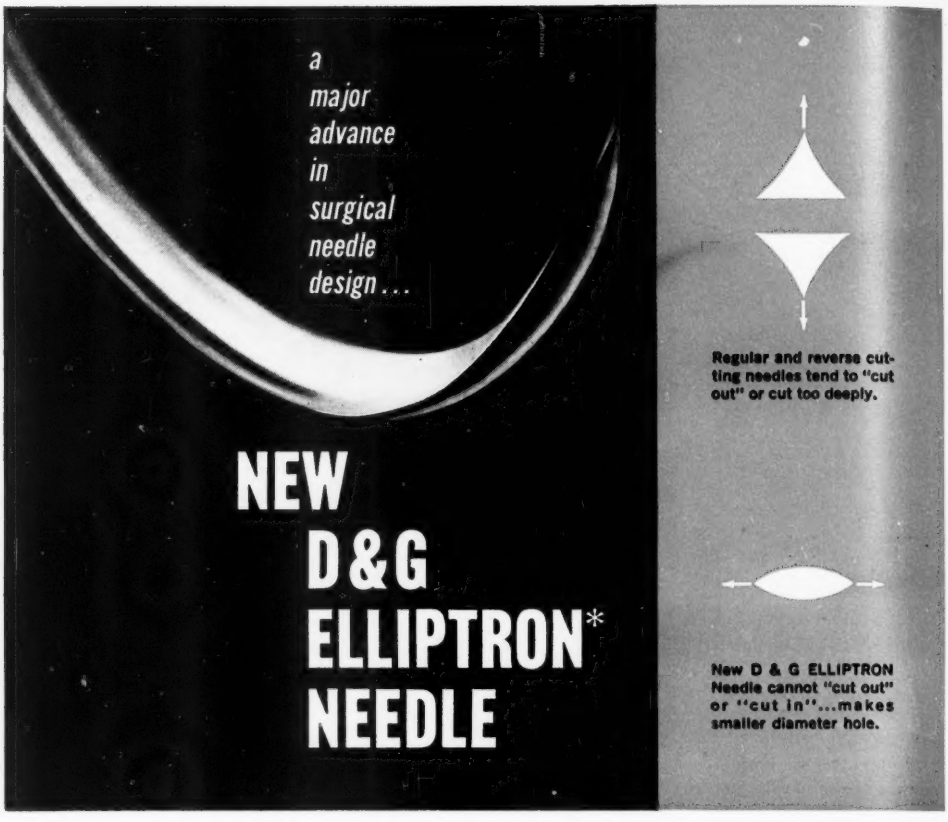
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A CRITICAL EVALUATION OF ANTICOAGULANT THERAPY IN PERIPHERAL VENOUS THROMBOSIS AND PULMONARY EMBOLISM

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DURING THE PAST TWO DECADES there has been considerable controversy concerning the value of anticoagulants in the management of peripheral venous thrombosis and its complications. Enthusiasm for vein ligation, thrombectomy, and sympathectomy has waned as reports have appeared questioning the effectiveness of these procedures in the prevention of pulmonary embolism. In recent years many investigators have concluded that anticoagulant therapy is the superior form of treatment for this disease. This report is an evaluation of the efficacy of anticoagulant therapy in the reduction of morbidity and mortality attending deep leg vein thrombosis and pulmonary embolism.

Since 1946 all anticoagulant therapy at the University of Michigan Hospital has been under the supervision of a team composed of representatives from the departments of medicine and surgery. A continuity in treatment policy has been maintained, largely through the efforts of one individual who was instrumental in the organization of this anticoagulant unit (I. F. Duff).

Initially, the only practical clinical method for the control of oral anticoagulant treatment was the Quick one stage estimation of "prothrombin time"; this method has been used throughout the study period. As other techniques for estimating anticoagulant effect have been developed, the results obtained with the newer methods (Owren P and P, Ware modification of the Owren method, two stage prothrombin test) have been compared with those provided by the standardized Quick procedure by Duff and associates. Empirically, the therapeutic range for the Quick one stage test has been a 2 to 2½ times prolongation of the control time or a "prothrombin activity" of 10 to 29 per cent. This criterion of effective response has been supported by Allen and DeLaughter and their associates. It has been claimed that an escape of "prothrombin activity" to 30 per cent or above has been associated with an increase in thromboembolic complications while a depression of "prothrombin activity" below 10 per cent has resulted in

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TABLE I.—DISTRIBUTION OF PATIENTS TREATED FOR THROMBOEMBOLISM

	Total group	*No operation*	*Post-operative*	*Male*	*Female*
Venous thrombosis without complication	313	148	165	147	166
Venous thrombosis with complication	46	22	24	27	19
Pulmonary embolism without complication	127	63	64	71	56
Pulmonary embolism with complication	25	12	13	19	6
Totals	511	245	266	264	247

TABLE II.—INCIDENCE OF HEART DISEASE

	No.	*Per cent*
Venous thrombosis		
Without complications	35 of 313	11.6
With complications	6 of 46	13.0
Pulmonary embolism		
Without complications	35 of 127	27.6
With complications	12 of 25	48.0

an inordinately high incidence of hemorrhagic complications. Likewise, on the basis of clinical experience, we adopted certain other objectives for an optimal course of treatment: (1) prompt initiation of anticoagulant effect with heparin until the "prothrombin activity" had been reduced to less than 30 per cent by an oral anticoagulant; (2) maintenance of anticoagulant effect for at least 3 days after subsidence of local pain and tenderness in the involved extremity *and* until ambulation had been fully established; (3) a minimal course of "effective therapy" of at least 10 days for venous thrombosis and 14 to 21 days for pulmonary embolism.

Since, on the basis of clinical experience, we have subscribed to the premises outlined, it has been our purpose in this study to evaluate critically the results obtained with our program of anticoagulant therapy.

METHODS

The data obtained for analysis were assembled from all of the available records of anticoagulant treatment from January 1, 1946 through December 31, 1955 on patients with acute deep venous thrombosis or pulmonary embolism. No attempt was made to differentiate between phlebothrombosis and thrombophlebitis since we have believed that these represent different manifestations of the same disease. The anticoagulant treatment record and the clinical chart provided the following information: name, age, sex, primary manifestation of the disease, associated diagnoses, any operation and its time relationship to the onset of thromboembolic disease, the duration of thromboembolism prior to the start of treatment, the drugs chosen for treatment, total duration of therapy, the number of days of treatment with "prothrombin activity" less than 10 per cent, between 10 and 29 per cent, between 30 and 39 per cent, between 40 and 49 per cent, and greater than 50 per cent, the type and time of occurrence of both thromboembolic and hemorrhagic complications. Any thromboembolic complication which was recognized or symptomatically presumed to have occurred within 12 weeks after cessation of treatment was considered as a complication of therapy. Fatal and nonfatal pulmonary emboli, extension of the thrombosis during treatment, or recurrence within the 12 week posttreatment interval were considered as complications of the disease which had not been prevented by the anticoagulant program.

The influence of a number of factors upon the complication rate has been assessed. The statistical evaluation of the differences which appeared was based on contingency tables with correction for continuity and on methods outlined by Snedecor for the test of independence in an R by C table. A probability value of less than .05 was accepted as indicative of a significant difference.

RESULTS

The records of 511 patients were studied. These patients were separated into two main groups on the basis of whether, at the time of initiation of treatment, the patient had leg vein thrombosis alone or had had a pulmonary embolus; it was expected that the latter group would have a higher complication rate and thus deserve special consideration. Both major groups were then subdivided into those treated without complication and those who developed a thrombo-

embolic complication during or after anticoagulants. Table I lists this information and relates it to operation and sex distribution.

The age distribution is similar to that noted in other studies of thromboembolism. The mean age in each of the 4 groups fell between 50 and 60 years, and 77.5 per cent of the total group were 40 years of age or older. No difference in age was found in a comparison between patients with an initial manifestation of venous thrombosis alone and those with pulmonary embolism or between those with complications as compared to those free of complications.

These patients presented a wide range of diseases in association with thromboembolism. Since the number of cases of any single disease was small, it was difficult to implicate specific entities with the occurrence of thromboembolism or the complications that occurred following anticoagulant treatment. However, 42 of the 511 patients had a fracture of the femur or tibia; the common association of thromboembolic disease with trauma to the lower extremity has been recognized by others. The incidence of complications of the thromboembolic disease was no higher in this group than in the group as a whole. Eighty-eight patients had some form of heart disease; the incidence of heart disease in the 4 subgroups is outlined in Table II. The higher incidence of associated heart disease in patients with pulmonary embolism represents a highly significant statistical difference (p = less than 0.005). The larger percentage of patients with heart disease in the group with pulmonary embolism who developed complications subsequent to the start of anticoagulant treatment approaches significance (p = less than 0.1 and greater than 0.05). The higher incidence of cardiac disease in association with pulmonary embolism has been supported by the autopsy studies of a number of investigators.

Sufficient information was available in the records of 404 patients to relate the interval between onset of clinical manifestations of thromboembolism and the institution of anticoagulant therapy to the distribution of therapeutic complications (other than hemorrhage). Fifty-seven per cent of this group were treated within 24 hours and 85 per cent within 7 days. There was no valid difference in duration of disease prior to therapy between those patients who developed complications and those who did not. This observation must remain presumptive since one must rely on the accuracy of history obtained and diagnostic acumen to define the time of onset. Venous thrombosis may exist for some time before giving rise to symptoms or signs, and even then may go unrecognized for a considerable period.

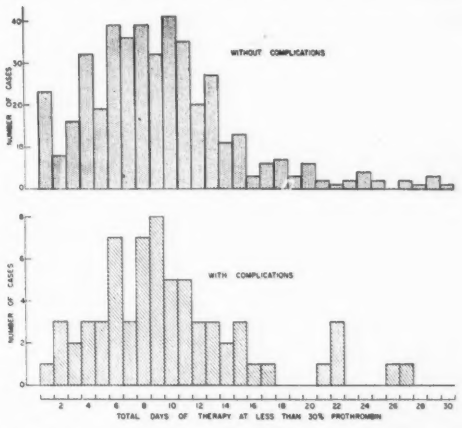

FIG. 1. Comparison of total days of "effective" therapy and incidence of thromboembolic complications.

A significant fraction of patients in this study developed thromboembolic disease in the postoperative period (Fig. 1). Forty-three per cent of this group had the onset of the venous thrombosis or pulmonary embolism within the first 7 postoperative days and 77 per cent within 14 days of operation. The peak incidence of the disease fell on the fourth and fifth postoperative days. The incidence declined progressively from 3 to 6 weeks postoperatively; all but 2 cases appeared within 6 weeks of operation. The occurrence of complications was not significantly influenced by the interval between operation and the onset of the disease.

TABLE III.—RELATION OF DURATION OF ANTICOAGULANT THERAPY TO COMPLICATION RATE

No. of days of effective therapy	*At less than 30 per cent prothrombin concentration* — *Complications* — *Present*	*Absent*	*Rate, per cent*	*At less than 40 per cent prothrombin concentration* — *Complications* — *Present*	*Absent*	*Rate, per cent*	*At less than 50 per cent prothrombin concentration* — *Complications* — *Present*	*Absent*	*Rate, per cent*
0– 7	27	210	10.9	13	144	8.3	11	125	8.1
8–10	17	106	13.8	23	112	17.0	16	113	12.4
11–14	11	73	13.1	14	104	11.9	21	108	16.3
>14	8	49	14.0	13	78	14.3	15	92	13.1
X^2 at 3° of freedom	0.39			4.80			4.29		

The duration of effective therapy does not seem to influence the complication rate at any of the 3 upper limits of "prothrombin activity" studied. For a probability of 0.05 at 3 degrees of freedom, $X^2=7.81$. Any smaller value indicates no statistical validity.

Heparin was the only agent given to 10 patients. Sixty-five per cent of the remaining 501 patients received heparin until a therapeutic effect had been achieved with the oral prothrombinopenic drugs. There was no significant difference in complication rate between the 175 patients who did not receive initial heparin treatment as compared to the 326 patients who did.

Of the 501 patients, 205 received bishydroxycoumarin (dicumarol®) and 265 phenylindandione (indon®). The others received a variety of prothrombinopenic agents of the coumarin and indandione series.

In an effort to evaluate the effect of "adequate" anticoagulant therapy on the incidence of complications, the number of days of treatment at a "prothrombin activity" of less than 30 per cent was tabulated and compared for the patients in each subgroup. Similar computations were made for the number of treatment days at any values less than 40 per cent and less than 50 per cent "prothrombin activity"; separate analyses at these higher "prothrombin activities" were carried out to see if the smaller number of patients than in the 0 to 7 day treatment period would have a higher incidence of complications. Table III is a condensation of this comparison. It demonstrates that the level of reduction of "prothrombin activity" does not appear to be important in the treatment of thromboembolic disease; none of the values differ significantly. Figure 1 shows the relationship between the number of days of "effective" treatment (at less than 30 per cent "prothrombin activity") and the distribution of patients with and without complication. There is a striking similarity in the duration of treatment of those patients treated successfully as compared to those who developed complications during or after anticoagulant therapy.

In order to assess the influence of the first few days of therapy on the thromboembolic complication rate, the number of days of "effective" therapy (i.e., less than 30 per cent "prothrombin activity") during (1) the first 5 days of treatment and (2) the first 10 days of treatment were tabulated. No significant difference in the rate of complications was seen in those patients having a well controlled early course of therapy as compared with those who escaped frequently to 30 per cent "activity" or above.

The thromboembolic complications of anticoagulant therapy are listed in Tables IV and V. During the course of anticoagulant medication, 25 pulmonary emboli occurred in 21 patients; 18 of these emboli appeared within the first week of treatment, 2 developed on the ninth and tenth days, and 5 occurred between the sixteenth and twentieth days. The embolic event led to death in 7 patients in this group, 4 of whom died within the first week of therapy.

After anticoagulant therapy had been completed, a presumptive diagnosis of pulmonary embolism was made in an additional 16 patients. The time of occurrence of these emboli was rather equally distributed over the period of 2 months after treatment. All patients dying within 12 weeks after conclusion of therapy were considered embolic deaths unless another cause was clearly established. There were 8 deaths possibly due to pulmonary embolism in this group.

Of the 6 deaths encountered in patients with venous thrombosis alone as the presenting manifestation of thromboembolic disease, 2 were sudden deaths occurring in patients receiving anticoagulant medication; in both instances, permission for autopsy

could not be obtained. One patient with an extensive carcinoma arising in the stomach received 50 to 100 milligrams of heparin per day for 4 days prior to death, a grossly inadequate form of treatment. The 3 deaths which followed cessation of anticoagulant drugs were the result of massive pulmonary emboli in nonambulatory patients with extensive metastatic neoplasm.

Of the 9 fatalities included in the group of patients with pulmonary embolism as the major presenting indication for anticoagulant treatment, 5 could not be attributed unequivocally to pulmonary embolism. Two patients died suddenly at home; 2 died suddenly in the hospital, but an autopsy was not permitted. An autopsy performed on the fifth patient demonstrated a recent myocardial infarct as well as a moderate-sized pulmonary embolus in one of the lobar arteries, and death could have been attributed to either. Of the remaining 4 deaths from pulmonary embolism, 1 occurred within 18 hours of the start of treatment; a second patient who was receiving anticoagulants at the time of death had had a vena cava ligation as well 2 days before; another patient died 6 days after completion of a 5 day course of depository heparin alone.

All of these deaths have been included in this evaluation of the effectiveness of anticoagulant treatment even though the cause of death was in doubt in 7 of the 15 and 5 other deaths were due to metastatic neoplasm.

Bleeding occurred in 14.8 per cent of the 540 courses of anticoagulant treatment (including second courses of therapy in patients who developed thromboembolic complications). There were no deaths from hemorrhage. Most of the hemorrhagic episodes were characterized by minor bleeding from the kidney, nose, or operative wound which did not interfere with continuation of treatment. Major bleeding developed in 2.4 per cent of the treatment courses. Eleven of these 13 instances of major bleeding appeared in an operative wound or at the site of a pre-existing gastrointestinal lesion. Cessation of the anticoagulant, administration of menadione bisulfite or vitamin K_1, and occasional blood transfusion controlled the hemorrhage in every case.

TABLE IV.—COMPLICATIONS DURING AND WITHIN 12 WEEKS AFTER ANTICOAGULANTS FOR VENOUS THROMBOSIS ALONE (359 PATIENTS)

	During treatment		*After treatment*		*Total*	
	No.	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
Extension of thrombosis	6	1.7	..	...		
Recurrent thrombosis	..	...	22	6.1		
Nonfatal pulmonary emboli	6	1.7	4	1.1	10	2.8
Fatal pulmonary emboli	3	0.8	3	0.8	6	1.6
All pulmonary emboli	9	2.5	7	1.9	16	4.4

DISCUSSION

The inherent difficulties in the diagnosis of thromboembolism present an uncontrollable variable which influences any clinical evaluation of this disease. No laboratory test is of any value in diagnosis. In some cases the paucity of symptoms and signs prevents an unequivocal diagnosis of either peripheral venous thrombosis or pulmonary embolism. Although pain and tenderness along the course of the deep veins, edema, and a palpable indurated vein frequently permit early recognition of deep venous thrombosis, these symptoms and signs are easily confused with manifestations of other diseases. The classical picture of pulmonary embolism—chest pain, pleural friction rub, dyspnea, and hemoptysis—is present in only about 15 per cent of autopsy—proved pulmonary embolism. The roentgenographic findings are highly variable; the presence of a wedge-shaped area of infarction is a rare exception rather than the rule. A minimal pleural fluid accumulation may be the only

TABLE V.—COMPLICATIONS DURING AND WITHIN 12 WEEKS AFTER ANTICOAGULANT TREATMENT FOR PULMONARY EMBOLISM PRIOR TO INSTITUTION OF THERAPY (152 PATIENTS)

	During treatment		*After treatment*		*Total*	
	No.	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
Extension of thrombosis	0	0	..	...		
Recurrent thrombosis	..	...	3	2.0		
Nonfatal pulmonary emboli	8	5.3	4	2.6	12	7.9
Fatal pulmonary emboli	4	2.6	5	3.3	9	5.9
All pulmonary emboli	12	7.9	9	5.9	21	13.8

evidence of even a massive embolus. Undoubtedly, some of the cases in this series have been included erroneously because of a mistaken diagnosis. However, we believe that the size of the sample involved in this evaluation is large enough to limit the sampling error based on equivocal diagnosis. It could be argued that those patients receiving a short period of therapy were individuals whose disease was minimal or nonexistent while those with complications represented extensive thrombosis which was inadequately treated. Although this reasoning may be valid and may account for a minor bias in sampling, it is more important to appreciate that the process of venous thrombosis in humans is variable in extent, manifestations, and duration of activity. The signs and symptoms of some unequivocal cases of venous thrombosis subside with 24 hours of initial heparin therapy, while, in other cases, they persist for weeks in spite of intensive treatment. With few exceptions, all patients in this series were treated until all clinical manifestations of the disease had disappeared; and some, particularly if they were not ambulatory, were kept on anticoagulants considerably longer.

Forty-seven per cent of the patients were treated for 7 or less days, and 72 per cent were treated for 10 or less days. Failure to attain our intended goal of a minimum of 10 days of treatment is attributed to the fact that the subsidence of signs and symptoms at variable intervals permitted the physician in charge of the patient to discontinue treatment and discharge the patient independent of the advice of the anticoagulant unit. This individualization of therapy is supported by the results of our analysis which does not show that the duration of anticoagulant administration has a critical influence on the rate of complications. Furthermore, there is no evidence to suggest that a specific period of treatment is necessary in order to minimize the occurrence of thromboembolic complications. Each patient should receive anticoagulant therapy until clinical signs and symptoms subside and until the patient is fully ambulatory. Our figures do indicate that one should be particularly cautious in providing adequate anticoagulant treatment in patients with coexisting heart disease who seem to have a greater propensity for developing embolic complications.

The duration of thromboembolic disease prior to the initiation of treatment did not influence the complication rate. The effectiveness of the early treatment program could not be related to the incidence of complications; similarly, there was no evidence to indicate that initial therapy with heparin until the oral anticoagulant had induced a therapeutic prothrombinopenia was critical in affecting the rate of complications. The 7 complications occurring during the first 3 days of treatment developed with equal frequency in those who did and those who did not receive initial heparin. Analysis of the entire series with regard to initial heparin administration suggested that a slightly higher complication rate existed in those patients who did not receive heparin, but this difference had no statistical validity.

It was not possible to ascertain the optimal level of "prothrombin activity" as determined by the Quick method that was necessary to minimize thromboembolic complications. Although we did attempt to evaluate the complication rate with all "prothrombin activity" values below 40 per cent and below 50 per cent, the majority of treatment days were in the range below 30 per cent. We hope that our present unselected alternate case study utilizing one group of patients maintained primarily in the 10 to 29 per cent treatment range and the other group in the 30 to 49 per cent range will ultimately provide us with more definitive data on comparative complication rates. Certainly the latter range would be more satisfactory if thromboembolic complications do not increase, since we believe it would lower the number of hemorrhagic complications. In the past several years the level of anticoagulation required for optimum protection has become an issue because the validity of the Quick procedure as

an accurate measure of changes in the clotting mechanism has been questioned. It has been proposed that anticoagulant dosage gauged by one of the newer test procedures (at a level corresponding to a "prothrombin activity" by the Quick method of 30 to 50 per cent) is equally effective, but no figures to support the contention that thromboembolic complications are no higher have been presented. It is well recognized that the Quick test does not quantitate prothrombin per se but is also influenced by changes in several other clotting factors (factor VII, perhaps some of the thromboplastin components). Furthermore, Alexander has demonstrated that the anticoagulant effects of the various drugs now in use are related not only to a depression of prothrombin but also to changes of a variable extent in one or several of these other components. Thus, it would seem more desirable to have a test which reflects changes in several of these clotting factors rather than in prothrombin alone. The observation by Duff and associates that a "therapeutic range" of 10 to 20 per cent by the Ware method compares with a range of 40 to 50 per cent by the Quick procedure has emphasized the need for caution in comparing the results and hazards of anticoagulant therapy when the administration of these drugs is controlled by different test methods.

The occurrence of a large proportion of the embolic complications in this series during the first week of anticoagulant therapy emphasizes the fact that anticoagulants are incapable of dissolving preformed thrombi. A friable, free-floating thrombus present prior to the initiation of anticoagulant treatment may still break off after therapy has been started. The proponents of superficial femoral vein ligation have used this fact as an argument for vein ligation as the treatment of choice; at the same time, they have ignored the demonstration of McLachlin and Paterson that over 50 per cent of leg vein thrombi are located at sites where bilateral superficial femoral vein ligation will not prevent pulmonary embolism. Perhaps, a combination of vein ligation and subsequent anticoagulant therapy would eliminate some of the disadvantageous factors and combine some of the advantages of both treatment regimens. However, this is merely a hypothesis and not a foregone conclusion. A large carefully controlled alternate case study would be necessary to prove or disprove the validity of this supposition.

What has anticoagulant therapy accomplished in the prevention of deaths from pulmonary embolism? This question cannot be answered with statistical accuracy because of the difficulties encountered in the clinical diagnosis of pulmonary embolism and because the accuracy of postmortem diagnosis varies with the care with which the autopsy is performed. A friable embolus may fragment at the bifurcation of the pulmonary artery into numerous microscopic emboli which may contribute to death but which are difficult to detect without examination of numerous sections of the lungs. Our figures suggest that, since clinical diagnosis has been so difficult, approximately only 1 patient in 8 with fatal or potentially fatal pulmonary emboli has received anticoagulant therapy. Secondly, anticoagulant therapy (or any other known form of treatment) has not prevented all deaths from pulmonary embolism. The "potentially fatal" pulmonary emboli, those emboli which would have resulted in fatality had anticoagulants not been used, have been calculated from the percentage of fatal emboli occurring in Cosgriff's compilation of American cases of venous thrombosis and embolism in which conservative treatment only was received. The fatal pulmonary emboli at our hospital were obtained from a review of the autopsy reports for a similar 10 year period, 1945 to 1954, during which time a mean autopsy rate of 68.6 per cent was obtained. If this embolic death rate had been calculated on the basis of 100 per cent autopsies, the percentage of patients receiving anticoagulant therapy would have been even smaller.

Although the results of any therapy in the prevention of death from pulmonary em-

bolism are dismal, we believe that anticoagulants have prevented death in 7 of every 10 patients whose venous thrombosis or nonfatal pulmonary embolus was recognized and treated when compared with the expected mortality attending the use of conservative measures alone.

Anticoagulants are of additional value in reducing morbidity during the early course of the disease. Their influence on postphlebitic sequelae is being assessed in a long term follow-up on the patients comprising this report. In Zilliacus' series of 214 patients with thromboembolism who received conservative treatment, 30 per cent of the patients developed venous thrombosis in the other lower extremity and 84 per cent had an extension of the original thrombotic process. The hospital stay was prolonged an average of 35.1 days. Anticoagulants have achieved an appreciable reduction in these complications (Tables IV and V), and a three to fourfold decrease in hospital stay. Barker reported a 43.8 per cent incidence of recurrent pulmonary embolism under conservative management and a 25.3 per cent incidence of embolism in patients receiving conservative treatment of venous thrombosis alone. Although these figures are not directly comparable, since they represent an earlier period of study, comparison even after two-fold reduction of these values to the data in Tables IV and V demonstrates a considerable decrease in complication rate with anticoagulant therapy.

SUMMARY

Venous thrombosis and pulmonary embolism remain a major complication of operation, trauma, and heart disease. An appreciable reduction in morbidity and mortality from thromboembolism must await more accurate clinical or laboratory diagnosis of this process or a rational, economically feasible program for mass prophylaxis.

Phlebothrombosis and thrombophlebitis are manifestations of the same disease entity. In patients in whom a clinical diagnosis of venous thrombosis or pulmonary embolism can be established, anticoagulant therapy can effect a significant reduction in morbidity and mortality. The experience of the University of Michigan Hospital with respect to this disease and its complication rate under a program of anticoagulant therapy has been presented. An evaluation of those factors which might influence the incidence of complications and the approach and problems relative to such an analysis have been discussed.

Thromboembolism continues to be "one of those diseases which demand minute study, because doubts still exist as to the nature of the affection, not withstanding the frequent opportunities which occur of observing it" (Trousseau, 1868).

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THE USE OF L-TRIIODOTHYRONINE AS A PITUITARY DEPRESSANT IN THE MANAGEMENT OF THYROID CANCER

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IT IS BECOMING increasingly apparent that the same hormonal stimuli that regulate normal thyroid growth and function may also be implicated in many types of human as well as experimental thyroid cancer. In the absence of thyrotropic hormone, involution of the thyroid gland occurs with decrease in size and weight and the development of low cuboidal epithelium. Despite this inactive appearance, there may be a slow turnover of iodine, and iodide transport into the gland appears to be affected by hormone which is stored or in process of being discharged.

There also appears to be a possibility of function and growth of the thyroid being independently controlled. A growth factor which seems to regulate cell height and gross size is apparently dependent upon the integrity of a certain area of the hypothalamus, for suitably placed hypothalamic lesions or intraocular transplantations of the pituitary gland result in thyroid atrophy, but iodine metabolism and production of thyroxin continues. A metabolic factor seems independent of the hypothalamus and enables the thyroid to concentrate and bind iodine. Both factors are regulated in part, at least, by the level of circulating thyroid hormone.

Conversely, an excess of thyrotropic hormone may serve as a promoting factor for thyroid neoplasms in the experimental animal. Most neoplasms so produced as well as a few occurring spontaneously remain dependent although some develop increasing autonomy.

Human thyroid cancer may display a somewhat similar relationship to thyrotropic hormone. As a result, in our experience a logical approach to the control of inoperable thyroid cancer has been by the suppression of pituitary thyrotropic hormone (6). This has usually been accomplished through the administration of desiccated thyroid, thyroxin, and more recently, l-triiodothyronine. Certain thyroid cancers have shown a remarkable alteration in their course following the removal of thyrotropic hormone stimulation. In some, inhibition of growth occurs but has been difficult to evaluate because of the well known chronicity of the disease. However, regression of the primary tumor and of lymph node, pulmonary, and bony metastases has been observed. At times, this has been most striking with roentgenographic disappearance of pulmonary metastases, improvement in ventilatory capacity, and regression and reossification of bony metastases with recovery from paraplegia. On the other hand, spontaneous regression in thyroid cancer has not been reported except by Crile in a patient with coincident hyperthyroidism.

In attempting to evaluate the dependency of thyroid cancer, not only must the biologic characteristics of the neoplasm be ascertained but criteria of adequate suppression of thyrotropic hormone must be established. While both desiccated thyroid and thyroxin have been employed to inhibit pituitary function, adequate suppression can only be inferred from radioiodine uptakes and clinical evidence of hyperthyroidism. The use

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TABLE I.—RESPONSE OF 10 PATIENTS WITH THYROID CANCER TO L-TRIIODOTHYRONINE

Patient Age Sex	*Type*	*Extent*	*Previous treatment*	*Duration of disease before rx. with T-3*	*Daily dose of T-3 (mcgm.)*	*Period of observation*	*I^{131} uptake by tumor*	*Suppression of I^{131} uptake by T-3*	*P.B.I. Initial*	*P.B.I. Final*	*Results of treatment*
M. F. 32 F	Papillary and alveolar	Lungs	Total thyroidectomy. Desiccated thyroid	2 years	200–300	6 months	yes	yes	2.7*	1.6	Decrease in pulmonary metastases (See Fig. 4)
E.A. 57 F	Papillary and alveolar	Lungs	Partial thyroidectomy. Desiccated thyroid	8 years	100–150	12 months	yes	yes	2.9*	2.3	No further progression of pulmonary metastases. (Initial dramatic response to desiccated thyroid, then progression until T-3 treatment)
C. S 34 F	Papillary and alveolar	Cervical nodes	Total thyroidectomy. Modified radical neck dissection. Desiccated thyroid	2½ yrs.	50–100	4 months	yes	yes	4.3†	1.6	No palpable tumor by clinical appraisal
A. F. 24 F	Papillary and alveolar	Thyroid	None	"Goiter"—2 yrs. Rx. for Graves' disease with x-ray, age 6	200–350	6 weeks	yes	yes	5.6‡	1.1	Reduction in size of gland by clinical appraisal. No further fall in P.B.I. after total thyroidectomy
O. R. 49 M	"Solid" tumor. No colloid production	Clavicle, vertebrae, lungs	Partial thyroidectomy. Desiccated thyroid	8 years	200	3 months	no	—	3.9	—	No response of metastatic tumor to either desiccated thyroid or T-3
M. W. 37 F	Papillary and alveolar	Thyroid cervical nodes	None	4 months	200–300	8 weeks	—	—	5.8	2.1	No conspicuous histologic changes at time of total thyroidectomy and neck dissection
G. W. 60 F	Alveolar	Thyroid cervical nodes	None	3 years	100	1 week	—	—	—	2.9	No histologic change at time of total thyroidectomy although P.B.I. had fallen
M. T. 50 F	Small celled (without colloid production)	Thyroid	Partial thyroidectomy	3–4 weeks	100	1 year	—	—	3.5§	1.6	Recurrence of tumor in cervical lymph nodes 3 weeks after lobectomy. (Tumor necrotic at time of neck dissection)
S. R. 79 F	Undifferentiated carcinoma	Thyroid	None	?	50	6 months	no	—	5.2§	1.7	No demonstrable recurrent or residual tumor
P.P. 62 F	Papillary and alveolar	Thyroid	Partial thyroidectomy 10 years previously	?	150	6 months	—	—	5.8§	<2.0	No demonstrable recurrent or residual tumor

*Patient myxedematous—P.B.I. reflects output of endogenous hormone by tumor.
†On desiccated thyroid, 2 gr. daily at this time.
‡Multifocal thyroid cancer, replacing entire thyroid gland.
§Treated by lobectomy with some normally functioning thyroid tissue on the opposite side present at this time.

of l-triiodothyronine for such a purpose has several advantages over other thyroid hormones by virtue of the immediacy and duration of its action as well as its apparent lack of firm binding by serum proteins.

Circulating thyroxin associates with a specific alpha globulin and while l-triiodothyronine is also bound by this protein, the bond is apparently somewhat weaker. This loose association with plasma proteins may account for its rapid disappearance into tissue spaces and its low plasma level. Consequently, athyreotic patients receiving l-triiodothyronine have serum protein-bound iodine levels in the range indicating myxedema when they are euthyroid. The administration of l-triiodothyronine has also been associated with a decrease in serum protein-bound iodine in euthyroid subjects.

This biochemical characteristic of l-triiodothyronine permits a quantitative measurement of endogenous thyroid hormone output (as serum protein-bound iodine) while a euthyroid or slightly hyperthyroid status is being maintained. The purpose of this investigation was to study the efficacy of l-triiodothyronine as a pituitary depressant and its effect on human thyroid cancer.

METHODS

Patients with thyroid cancer were appraised for type, extent, and functional activity of their neoplasm and their metabolic status determined by clinical evaluation in conjunction with determination of serum protein-bound iodine and uptake of radioiodine. L-triiodothyronine was then administered by mouth in divided doses beginning at 25 micrograms twice daily with increasing increments at 1 to 2 week intervals until tolerance or a level of 200 to 300 micrograms daily. This dosage was continued for periods from 6 weeks to 1 year or more. Periodic determinations of the serum protein-bound iodine reflecting the endogenous output of thyroid hormone were procured during the course of the study.

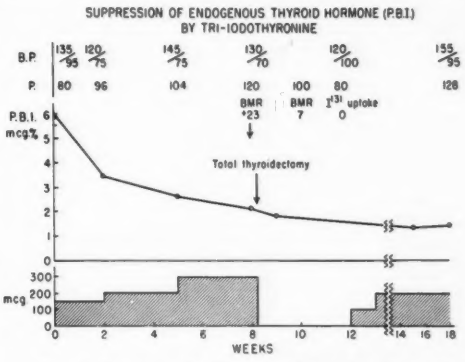


FIG. 1. Response of a 37 year old female to increasing amounts of l-triiodothyronine over an 8 week period. Slight hyperthyroidism as evidenced by increase in pulse and blood pressure seemed present at 300 micrograms daily. Following total thyroidectomy and right radical neck dissection for carcinoma, there was no evidence of I^{131} retention and therapy with l-triiodothyronine (200 mcgm. daily) was resumed (see Figs. 6, 7, and 8).

These findings were correlated with gross changes in the primary or metastatic neoplasm and when possible with uptake of radioiodine. In those patients with an operable lesion, thyroidectomy was performed after an appropriate interval and both normal thyroid and neoplasm appraised for morphologic changes.

Metabolic activity of the normal, nodular, and cancerous thyroid was also appraised by determining the incorporation of radiophosphorus administered intravenously 24 hours before surgery as sodium hypophosphate. At the time of operation, biopsy specimens of tumor, normal thyroid, and adjacent sternocleidomastoid muscle were weighed to 0.10 milligram, baked at 125 degrees centigrade for 24 hours, and their radioactivity per unit weight was determined. Activity was expressed as a ratio of counts per minute per milligram of tumor to counts per minute of 0.01 milliliter of serum. The P^{32} activity in tissues studied was considered by Barnum to reflect the rate of synthesis of nucleic acids and serve as a measure of the metabolic activity of the thyroid cell. Thyrotropic hormone suppression was evaluated indirectly by appraisal of serum protein-

‡Multifocal thyroid cancer, replacing entire thyroid gland.
§Treated by lobectomy with some normally functioning thyroid tissue on the opposite side present at this time.

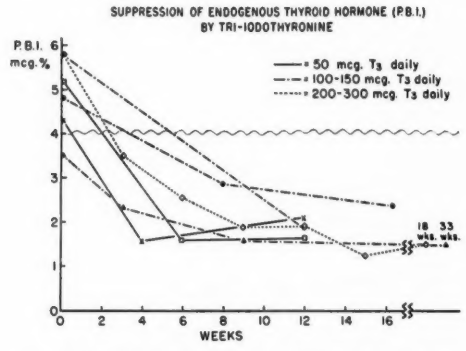


FIG. 2. Effect of various amounts of l-triiodothyronine on the endogenous output of thyroid hormone in patients with thyroid cancer.

bound iodine levels, radioiodine uptake, incorporation of P^{32} into the thyroid, and morphologic changes in the thyroid. By comparing functional and morphologic alterations in normal and cancerous thyroid tissue, the dependent status of thyroid neoplasms was determined.

RESULTS

Ten patients with thyroid cancer in various stages of disease, i.e., localized to thyroid or with lymph node, pulmonary, and bony metastases, were suitable for study (Table I).

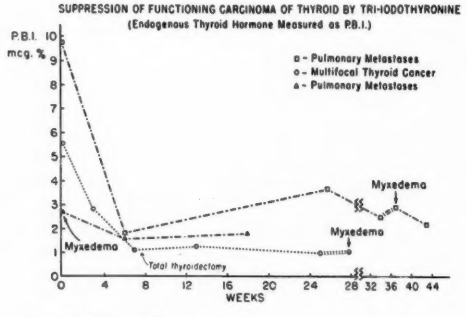


FIG. 3. Effect of l-triiodothyronine on the output of thyroid hormone (P.B.I.) by functioning thyroid cancer. The P.B.I. level of 9.0 represents response to desiccated thyroid. Subsequent levels of P.B.I. are on the basis of functioning thyroid cancer.

PROTEIN-BOUND IODINE

The administration of l-triiodothyronine to euthyroid patients with thyroid cancer was characterized by a fall in the endogenous output of thyroid hormone (serum protein-bound iodine). The decrease in serum protein-bound iodine was progressive until by 6 weeks it was well into the hypothyroid range (Fig. 1). The rate of fall is similar to the normal thyroxin degradation pattern. There was usually no subsequent fall despite an increase in dosage or longer intervals of time. That this level represented fairly complete inhibition of the pituitary effect is reflected by the lack of further decrease subsequent to total thyroidectomy. From the data at hand, it is difficult to determine the minimal dosage required for thyrotropic hormone suppression (Fig. 2). In some individuals, it is apparently as little as 50 micrograms daily.

Only 1 patient failed to have depression of the protein-bound iodine below 2.0, and this was in an individual with pulmonary metastases that had exhibited increasing autonomy of growth. This elevated protein-bound iodine suggests some autonomy of function similar to the findings in Graves' disease where exogenous thyroid hormone does not cause significant suppression of radioiodine uptake or endogenous thyroid hormone output. However, failure to suppress iodine uptake in patients with functioning cancer was not observed.

Two patients in whom a total thyroidectomy had previously been performed and who had functioning pulmonary metastases capable of manufacturing an iodinated protein exhibited a fall in this iodinated protein after institution of l-triiodothyronine therapy (Fig. 3). In 1 patient, this was nicely correlated with decrease in size of pulmonary metastases (Figs. 4 and 5).

In all patients other factors known to depress protein-bound iodine values such as cirrhosis or the administration of cortisone or ACTH were not present.

The tolerance to the drug is quite variable with a few patients exhibiting symptoms of

hyperthyroidism as manifested by nervousness, tachycardia, and heart consciousness at levels of 100 to 150 micrograms daily and others showing no such symptoms at 200 to 350 micrograms daily. Contrary to experimental studies in the animal by Barker but in keeping with other clinical observations by Asper, the action of l-triiodothyronine persists for several days after its withdrawal. Furthermore, there seems to be no ill effect with administration once or twice daily instead of every 8 hours.

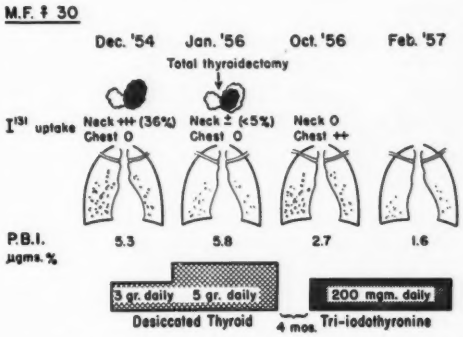


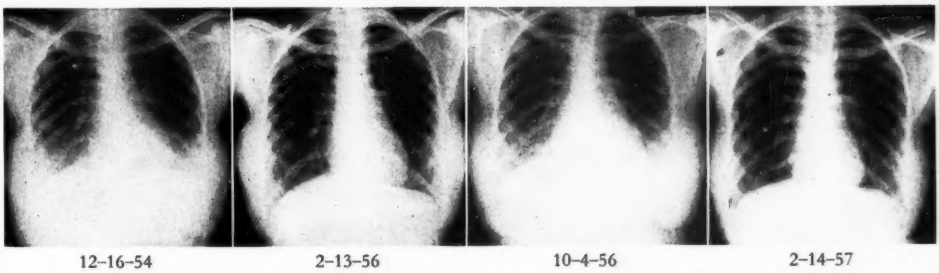
FIG. 4. Course of a 31 year old female with papillary and alveolar adenocarcinoma of the thyroid with pulmonary metastases. Pulmonary metastases decreased by roentgenographic examination (Fig. 5) after the administration of desiccated thyroid and reappeared with the development of myxedema. Regression again occurred after the administration of l-triiodothyronine and return to a euthyroid or slightly hyperthyroid status.

RADIOIODINE UPTAKE

Suppression of radioiodine uptake was readily accomplished in all patients in whom there was functioning carcinoma. Due to the diffuse metastatic involvement of the thorax and difficulty in procuring an appraisal of the entire region, this could not be expressed as per cent depression, as is frequently done over the thyroid area. In no instance was any autonomy of iodine uptake retained, similar to that seen in Graves' disease. The suppression of I^{131} uptake in the euthyroid patient by l-triiodothyronine has already been well documented.

MORPHOLOGIC CHANGES

Morphologic changes in the normal thyroid gland after thyrotropic hormone suppression for greater than 1 year are characterized by involution and atrophy. There appears to be little difference histologically between the effect of desiccated thyroid and l-triiodothyronine. A comparison of the effects of l-triiodothyronine reveals involution of the normal gland (Fig. 6) to be greater than that of the neoplastic gland (Figs. 7 and 8). Whereas normal acini are characterized by low cuboidal epithelium with some evidence of colloid production, the neoplastic cells on the contrary are somewhat more columnar with no associated colloid. It may well be that with a longer lapse of time greater morphologic changes in the neoplasm will be seen. On the other hand, we have observed a conspicuous desmoplastic reaction of 1 primary tumor after 8 weeks of therapy. This may, however, represent a primary sclerosing characteristic of the thyroid tumor.



12–16–54 2–13–56 10–4–56 2–14–57

FIG. 5. Sequential chest x-ray films in a 31 year old female illustrating response of metastatic tumor to hypophysial suppression (see Fig. 4).

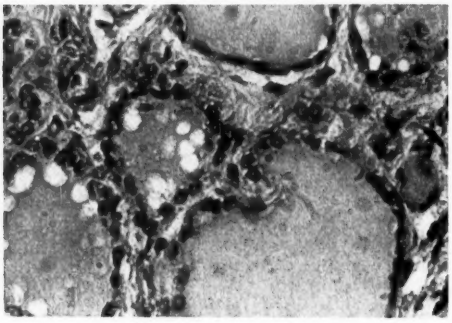


FIG. 6. Pattern of normal thyroid after 8 weeks of suppression by l-triiodothyronine exhibits both active and inactive acinar epithelium but no hyperplasia or thyroiditis (see Fig. 1).

P^{32} INCORPORATION INTO NORMAL AND NEOPLASTIC THYROID

Pilot observations on the incorporation of P^{32} into neoplastic tissue suggest that it has a greater degree of metabolic activity than does the normal thyroid (Table II). The activity of the normal thyroid expressed as counts per minute per milligram averages 5.5 as compared to patients with Graves' disease controlled only by propylthiouracil or 2-mercapto-imidazole with an activity of 15. The P^{32} activity of thyroid cancer approximates that of the hyperplastic gland. When normal thyroid and thyroid cancer are "inhibited" in the same patient by l-triiodothyronine, the P^{32} activity of the normal gland is apparently more readily suppressed than is the neoplasm.

TABLE II.—P^{32} UPTAKE IN NORMAL, HYPERPLASTIC, AND NEOPLASTIC THYROID GLANDS

Patient (age, sex)	*Serum c.p.m./.01 ml.*	*Thyroid (dry wt.) c.p.m./mgm.*	*Thyroid/serum ratio*
Normal			
33 M.....	3.1	4.6	1.5
80 M.....	3.4	8.3	2.4
47 M.....	1.6	4.1	2.6
38 F.....	4.5	6.8	1.5
Hyperplastic			
30 F.....	3.1	22.9	7.5
37 F.....	3.0	23.8	7.8
20 F.....	2.5	11.6	4.6
33 F.....	2.0	5.2	2.8
Carcinoma			
50 F.....	3.2	24.3	7.56
49 M.....	—	18.9	—
Carcinoma (Rx with T-3)			
60 F (1 week)..	2.3	19.3	8.6
23 F (7 weeks).	2.3	10.3	4.4
37 F (8 weeks).	3.0	17.3	5.8

Specimens from normal thyroid glands were procured from patients being operated upon for diseases unrelated to the thyroid. Specimens from hyperplastic glands were procured from patients with Graves' disease brought to a euthyroid status with either propylthiouracil or 2-mercapto-imidazole (see text for methods).

DISCUSSION

The recognition that papillary and alveolar thyroid cancer may be dependent upon upon thyrotropic hormone for continued growth and function has led to the palliative treatment of this disease by the administration of exogenous thyroid hormone. Direct criteria for measuring thyrotropic hormone suppression are lacking and must be inferred by observing the resultant effect on the end organ, the thyroid gland. The suppression of radioiodine uptake,[1] the fall in output of endogenous thyroid hormone (protein-bound iodine), and the atrophy of the gland histologically that occur following l-triiodothyronine all support the loss of thyrotropic hormone. The fall in the protein-bound iodine is somewhat comparable to that seen following hypophysectomy for breast cancer, and approximates the degradation curve of thyroid hormone. The protein-bound iodine values following hypophysectomy are essentially the same as those after l-triiodothyronine therapy. Whereas all thyroid hormones will apparently suppress pituitary function, l-triiodothyronine seems superior in that it permits measurement of the endogenous output of thyroid hormone as protein-bound iodine thus giving a quantitative index of pituitary and thyroid suppression.

The thyroidal atrophy as well as fall in radioiodine uptake which occurs following the administration of l-triiodothyronine seems comparable in every respect to that following other exogenous thyroid hormones. The incorporation of P^{32} by the thyroid would also seem to serve as a fairly

[1]This may be a direct effect upon the iodide pump rather than via the pituitary gland since thyroid hormones produced a more profound inhibition of the thyroidal iodide pump than does hypophysectomy.

reliable index of thyrotropic hormone activity, and Borrell and Almarholmgren have shown that its level reflects both function and growth activity as measured by increase in cell height and synthesis of thyroid hormone. The observations in these individuals seem to confirm the experimental findings in animals that the P^{32} level in the thyroid gland is lowered during the administration of exogenous thyroid hormone.

Most of the criteria employed for thyroid activity are those concerned with function and only by inference is there alteration in growth as well. Whether P^{32} activity is an index of growth as well as function can only be ascertained by further study and correlation with histologic changes.

While for the most part, growth and function seem to correlate well and are regulated primarily by thyrotropic hormone level, certain clinical observations would tend to confirm the experimental evidence that there may be factors independently controlling function and growth. Independent control of function and growth would certainly be in keeping with the behavior of most thyroid cancers. While metastases occur and may even be widespread, it is most unusual to have hyperfunction of these metastases with resulting hyperthyroidism. Yet, these metastases are quite capable of responding to the demands of the organism and to yielding an increased output of thyroid hormone and maintenance of a euthyroid state following removal of all normally functioning thyroid tissue.

Thus, a normal "feed back control" seems to be operating over function and output of thyroid hormone. Growth, on the other hand, does not seem so completely controlled since in the euthyroid state with presumed normal levels of thyroid hormone, metastases develop and increase in size. That some control or dependency of growth does exist, however, is demonstrated by the response to either increased or decreased levels of thyrotropic hormone. Thus, the functional response of thyroid neoplasm seems wholly controlled by the usual mechanisms of normal thyroid regulation. Growth, on the other hand, though dependent in part on thyrotropic hormone, does possess autonomy that seems to be progressive. Whether suppression of function of a neoplasm as measured by depression of radioiodine uptake and fall in the endogenous output of thyroid hormone is also evidence of maximal suppression of growth stimulus is not clear. It apparently is true insofar as normal thyroid tissue is concerned.

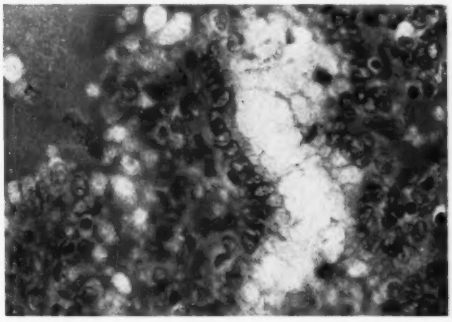


FIG. 7. Papillary and alveolar thyroid cancer was present upon biopsy of cervical lymph node. Note cell height.

All tumors except those showing no histologic similarity to normal thyroid (for example, spindle cell and giant cell sarcoma) will probably prove to have some degree of

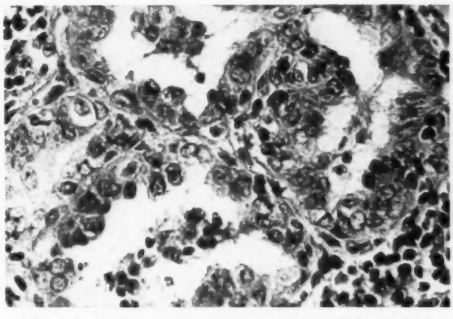


FIG. 8. Eight weeks after initiation of l-triiodothyronine, a total thyroidectomy disclosed papillary tumor in additional lymph nodes as well as the thyroid gland. Cell height is little changed over that on previous lymph node biopsy. All tumor is predominantly papillary with no colloid production.

dependency upon thyrotropic hormone, and it is likely that this can be correlated with the tumor's ability to "trap" iodine. This has already been nicely demonstrated in the experimental animal by Wolman and associates. Two factors would seem to militate against employing the uptake of radioiodine in human tumors as a criterion of dependency. When there is competition with the normal functioning thyroid gland, the neoplasm may show negligible I^{131} uptake and secondly, growth and metabolism of cancer, as is apparently true for normal thyroid, may be independently controlled.

SUMMARY

The administration of l-triiodothyronine is a simple and effective means of depressing the output of thyrotropic hormone by the anterior pituitary as measured by the loss of function and atrophy of the normal thyroid gland. It is considered superior to other thyroid hormones in this regard because its biochemical characteristics permit a quantitative measurement of endogenous thyroid hormone output and, by inference, thyroid inhibition. In the treatment of patients with thyroid cancer by the administration of exogenous thyroid hormone, the use of l-triiodothyronine permits a more accurate and quantitative measurement of pituitary gland suppression. The response of thyroid cancer seems similar to that observed when other means of pituitary inhibition are employed.

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COMPARISON OF COMPLICATIONS FOLLOWING INTESTINAL SURGERY AFTER ORAL AND PARENTERAL PREOPERATIVE ANTIBIOTIC PREPARATION

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OPERATIONS CAN BE PERFORMED SAFELY on the intestines after the use of parenterally administered antibiotics which do not alter the intestinal bacterial flora, and the mortality and morbidity figures when such a regimen is used compare favorably with those when the preparative regimen provides for administration of antibiotics to decrease or eliminate the intestinal bacteria. A consecutive unselected series of 261 patients who had various types of intestinal operations at the Mayo Clinic after the parenteral use of penicillin and dihydrostreptomycin will be compared with a fairly comparable series of 243 patients who underwent various intestinal operations after the oral administration of members of the tetracycline group of antibiotics. Micrococcic enteritis did not occur in the patients whose intestinal bacteria were not altered by orally administered antibiotic agents. This contrasts with the incidence of micrococcic enteritis following the use of tetracycline derivatives reported in our institution by Pettet, Judd, and Dearing (4) and Dearing, Heilman, and Sauer (1, 2), and in other medical centers by Janbon and Reiner and associates.

METHODS

The patients included in this study were divided into three groups according to the antibiotic they received preoperatively (Table I). The first group received 4 average doses of 750 milligrams of chlortetracycline by mouth each day for 3 to 4 days before operation. The second group received oxytetracycline by mouth in average doses of 500 to 750 milligrams, 4 times a day for 3 to 4 days before operation. Patients in both of these groups received penicillin or a combination of penicillin and dihydrostreptomycin on the day of operation and daily thereafter for a variable period depending on the postoperative course. The third group was given parenterally 0.5 gram of streptomycin, 0.5 gram of dihydrostreptomycin, and 400,000 units of penicillin on the evening before operation and received daily 1 gram of streptomycin, 1 gram of dihydrostreptomycin, and 800,000 units of penicillin for varying periods after operation; the time this dosage was continued depended on progress. No antibiotics were given by mouth to this group of patients. For the sake of brevity, this group will be referred to as the penicillin-dihydrostreptomycin group.

In preparation for operation, patients in all groups received a minimum-residue diet after entering the hospital. Mechanical cleansing of the bowel was accomplished by giving sodium phosphate (phospho-soda) for 2 to 3 days before operation, and enemas the evening before operation. Rectal aspiration was employed the next morning prior to the operation.

Excluded from these groups were a small number of children and a few adult patients who had received antibiotics or mixtures of antibiotics other than those recorded in our study.

The operative procedures were performed by one surgeon (J. M. W.) and consisted of combined abdominoperineal resection,

From the Sections of Medicine and Surgery, Mayo Clinic and the Mayo Foundation, Rochester, Minnesota.

TABLE I.—DISTRIBUTION OF CASES

	Chlortetracycline by mouth	*Oxytetracycline by mouth*	*Penicillin-dihydrostreptomycin parenterally*
Combined abdominoperineal resection	15	15	21
Anterior resection	38	31	76
Combined abdominoperineal with endo-anal anastomosis	19	22	27
Partial resection of colon			
Right hemicolectomy	20	12	49
Left hemicolectomy	7	8	18
Resection of transverse colon	0	2	2
Subtotal colectomy	10	4	9
Total colectomy	3	6	8
Colostomy	4	3	13
Closure of colonic stoma	7	2	10
Miscellaneous	12	3	28
Totals	135	108	261
	243		

See text for detailed explanation of the antibiotics given.

anterior resection, combined abdominoperineal resection with endo-anal anastomosis (pull-through operation), partial resection of the colon, subtotal colectomy, total colectomy, colostomy, closure of colonic stoma, or some miscellaneous procedure. The intestinal anastomoses were done by the closed method over a three-bladed clamp.

In evaluating the relative effectiveness of these three different preparations in preventing postoperative complications only those factors which might possibly be affected by the administration of these various antibiotics have been considered. We have not included in our study such complications as postoperative atelectasis, transurethral resection during the postoperative period, revision of ileac stoma, and other isolated complications which did not seem to be related etiologically to any effect of the antibiotics. Since blood-clotting mechanisms may conceivably be affected by antibiotics, we have included in our study both phlebitis and pulmonary embolism.

In listing the complications, the term "wound infection" refers to superficial sepsis of the wound unless specifically indicated otherwise; fever of undetermined origin applies to any temperature of 100 degrees F. or more which persisted longer than 24 hours. Phlebitis means an inflammation of the deep venous system unless otherwise stated.

Median number of hospital days after operation is used as an index of morbidity. It means that 50 per cent of the patients had a hospital stay less than, and 50 per cent had a hospital stay greater than, the median number of hospital days stated for that group.

POSTOPERATIVE COMPLICATIONS AND DEATHS

Various operative procedures. The incidence of several postoperative complications which developed among patients who received tetracycline derivatives by mouth or penicillin and dihydrostreptomycin by parenteral injection prior to combined abdominoperineal resection and prior to anterior resection is compared in Table II. One death occurred in the group receiving oxytetracycline before anterior resection,

TABLE II.—COMPLICATIONS AFTER COMBINED ABDOMINOPERINEAL RESECTION AND ANTERIOR RESECTION

	Chlortetracycline by mouth	*Oxytetracycline by mouth*	*Penicillin-dihydrostreptomycin parenterally*
COMBINED ABDOMINOPERINEAL RESECTION			
Total cases	15	15	21
Median days in hospital after operation	34	31	24
Complications			
Wound infection	0	1	0
Fever of undetermined origin	0	3	1
Pneumonia	0	1	0
Phlebitis	1	1	0
Total	1	6	1
Deaths	0	0	0
ANTERIOR RESECTION			
Total cases	38	31	76
Median days in hospital after operation	14	15	17
Complications			
Wound infection	0	2	3
Fever of undetermined origin	3	1	3
Fecal fistula	0	2	9
Enterocolitis	0	1*	0
Phlebitis	2	0	0
Pulmonary embolus	0	1*(?)	1
Sigmoidocutaneous fistula	0	1	0
Peritonitis	0	0	1*
Total	5	8	17
Deaths	0	2	1

*Died.

which was attributed to pseudomembranous enterocolitis. This was the only case in our study in which the diagnosis of enterocolitis was made.

CASE 1. A 59 year old woman had been subjected to anterior resection for multiple (3) polyps of the sigmoid colon. Twenty-four hours after operation profuse watery diarrhea, hyperperistalsis, increase in pulse rate, fever, and clinical evidence of shock developed. The patient died 24 hours later. Pulmonary edema was a terminal event. Clinically, the findings were those of pseudomembranous enterocolitis. Necropsy was not obtained.

The second death which occurred in the oxytetracycline group after anterior resection probably was due to pulmonary embolism.

CASE 2. A 67 year old woman was admitted to the hospital with a diagnosis of carcinoma of the upper part of the rectum. She was obese and hypertensive, the blood pressure was 204 millimeters of mercury systolic and 110 millimeters diastolic, and the ocular fundi showed evidence of hypertension, group 3. Anterior resection was performed. The patient did well until she collapsed suddenly on the fifth postoperative day. The cause of death was undetermined but was thought to be pulmonary embolism. Necropsy was not obtained.

One death occurred in the penicillin-dihydrostreptomycin group after anterior resection.

CASE 3. A 62 year old man had undergone palliative anterior resection for scirrhous adenocarcinoma of the upper part of the rectum with metastasis to the liver. He did well until the tenth postoperative day when his temperature rose to 103 degrees F., and abdominal distention and tenderness developed. Bowel sounds were absent, and he passed nothing by rectum. His condition continued to worsen and over the next 2 weeks dependent edema, progressive jaundice, and anuria developed. He lapsed into coma and died on the thirty-sixth postoperative day.

Necropsy revealed a separation of the suture line posteriorly, a retroperitoneal abscess containing approximately 300 cubic centimeters of pus, and generalized peritonitis. Cultures taken from the abscess cavity revealed Pseudomonas (species?) and Proteus (species?). In addition, there were metastatic lesions in the liver and peripancreatic nodes and in the lungs and hilar nodes.

Most of the complications among patients undergoing combined abdominoperineal, sphincter-preserving operations (pull-through operations) were minor but all three of the major complications resulted in the death of the patient (Table III). One death occurred among each group of patients as follows:

TABLE III.—COMPLICATIONS AFTER COMBINED ABDOMINOPERINEAL RESECTION WITH ENDO-ANAL (PULL-THROUGH) ANASTOMOSIS AND PARTIAL RESECTION OF COLON

	Chlortetracycline by mouth	*Oxytetracycline by mouth*	*Penicillin-dihydrostreptomycin parenterally*
COMBINED ABDOMINOPERINEAL RESECTION WITH ENDO-ANAL ANASTOMOSIS			
Total cases	19	22	27
Median days in hospital after operation	23	31	23
Complications			
Wound infection (abdominal)	0	0	1
Wound infection (posterior)	1	0	4
Fever of undetermined origin	2	2	2
Pneumonia	0	1	0
Phlebitis	0	0	1
Pulmonary embolus	1*	1*(?)	0
Peritonitis	0	0	1*
Total	4	4	9
Deaths	1	1	1
PARTIAL RESECTION OF THE COLON			
Total cases	27	22	69
Median days in hospital after operation	15	15	17
Complications			
Wound infection	0	1	4
Fever of undetermined origin	2	1	2
Pneumonia	0	0	1
Phlebitis	1	1	2
Pulmonary embolus	0	0	1
Pelvic abscess			1
Deep wound infection			1
Psoas abscess on right			1
Subdiaphragmatic abscess			1*
Peritonitis			1*
Total	3	3	15
Deaths	0	0	2

See Table I for details.
*Died.

CASE 4. A 56 year old woman had a pull-through operation for carcinoid of the rectum and polyp of the upper part of the sigmoid. The hospital course was uneventful until the fourteenth postoperative day when she suddenly collapsed while eating breakfast and died a few minutes later. Necropsy revealed massive bilateral pulmonary embolism.

CASE 5. A 55 year old woman was operated on for subacute nonspecific ulcer with stricture 5 centimeters above the anal margin. She did well until the seventh postoperative day when she collapsed while returning to her bed from the bathroom. She responded only

TABLE IV.—COMPLICATIONS AFTER SUBTOTAL COLECTOMY AND TOTAL COLECTOMY

	Chlortetracycline by mouth	*Oxytetracycline by mouth*	*Penicillin-dihydrostreptomycin parenterally*
SUBTOTAL COLECTOMY			
Total cases	10	4	9
Median days in hospital after operation	15	16	16
Complications			
Fever of undetermined origin	2	0	0
Phlebitis	0	0	1
Total	2	0	1
Deaths	0	0	0
TOTAL COLECTOMY			
Total cases	3	6	8
Median days in hospital after operation	18	33	45
Complications			
Fever of undetermined origin	0	1	0
Phlebitis	0	1	3
Peritonitis	0	0	1*
Total	0	2	4
Deaths	0	0	1

*Died.

slightly to treatment and died within a few hours. The clinical picture favored pulmonary embolism. Necropsy was not obtained.

CASE 6. A 70 year old man was operated on for adenocarcinoma, grade 2, of the rectum. The patient was obese and diabetic, and had coronary heart disease. He did well until the third postoperative day when he had some evidence of cardiovascular collapse with sweating, increase in pulse rate, and decrease in blood pressure. High fever and evidence of peritonitis developed and he died on the fifth postoperative day. Postmortem examination revealed gangrene of the lowermost segment of the colon just above the anastomosis with separation of the suture line and generalized peritonitis. Routine cultures of purulent material from the anterior surface of the small bowel obtained at necropsy were reported as negative for growth of microorganisms.

All of the major complications after hemicolectomy occurred in the penicillin-dihydrostreptomycin group (Table III). Two deaths occurred among these patients. One death was associated with subdiaphragmatic abscess; the other with generalized peritonitis.

CASE 7. A 62 year old diabetic woman was referred to the clinic for treatment of an ileocutaneous fistula which had followed appendectomy 2 months previously. It was necessary to resect the terminal ileum and perform an end-to-end ileocolostomy. Postoperative recovery was slow and complicated by some congestive heart failure, distention of the intestines, and considerably delay in tolerating oral feedings. On the fourteenth postoperative day the patient had some serosanguineous drainage from the incision indicating some separation of the deeper layers of the wound. Adhesive strapping was applied and healing of the wound progressed satisfactorily. On the thirty-second postoperative day pain developed in the chest and back on the left side, and temperature rose to 102 degrees F. This septic course continued despite treatment with antibiotics. Blood cultures were negative. Although subdiaphragmatic abscess was suspected, it was not until the forty-eighth postoperative day that the diagnosis was definitely established with the aid of fluoroscopic examination. The abscess was drained and the temperature subsided. Cultures of material from the abscess revealed Micrococcus pyogenes which was sensitive to penicillin. The patient was given penicillin and did well until 6 days later when the temperature rose to 101 degrees F. Nine days after drainage of the abscess, dyspnea, cyanosis, and evidence of acute heart failure developed, and the patient died. At necropsy, cultures taken from the region of drainage of left subdiaphragmatic abscess revealed Aerobacter aerogenes and Candida albicans. Also, there were multiple abscesses in the spleen and left kidney from which Aerobacter aerogenes, Micrococcus pyogenes, and Escherichia coli were cultured. Gangrene of the terminal ileum and cecum and gas gangrene of the mucosa of the ileum were found although these tissues were still intact.

CASE 8. A 73 year old man underwent abdominal exploration for a large mass in the right lower quad-

TABLE V.—COMPLICATIONS AFTER COLOSTOMY AND CLOSURE OF COLONIC STOMA

	Chlortetracycline by mouth	*Oxytetracycline by mouth*	*Penicillin-dihydrostreptomycin parenterally*
COLOSTOMY			
Total cases	4	3	13
Median days in hospital after operation	15	16	16
Complications			
Wound infection	0	0	1
Fever of undetermined origin	1	0	0
Fecal fistula	0	1	0
Pulmonary embolus	0	1*	0
Total	1	2	1
Deaths	0	1	0
CLOSURE OF COLONIC STOMA			
Total cases	7	2	10
Median days in hospital after operation	12	18	23
Complications			
Wound infection	0	0	2
I ..al fistula	0	0	3
Total	0	0	5
Deaths	0	0	0

*Died.

rant. A reticulum cell sarcoma arising in the cecum with extensive nodal involvement was found. There was an associated abscess about 6 inches in diameter posterior to the cecum. The entire ileum, a small portion of the jejunum, and the right part of the colon were removed and an end-to-end jejunocolostomy was performed. The immediate postoperative course was satisfactory and the patient regained function of the gastrointestinal tract for a time and was able to eat. By the tenth postoperative day, however, vomiting, abdominal distention, and peripheral edema developed, urinary output decreased, and the patient lapsed into coma. The serum proteins were low and despite transfusions and albumin by vein they failed to rise appreciably. Tube feedings were not tolerated. The patient died on the twentieth postoperative day. Necropsy revealed generalized fibrinopurulent peritonitis from which Escherichia coli and Aerobacter aerogenes were cultured. Metastatic lesions were found in the small intestine, regional nodes, pancreas, adrenal glands, thyroid, and bladder.

Subtotal colectomy was performed in most instances for chronic ulcerative colitis or polyposis. There were no serious complications following this operation (Table IV).

The incidence of complications among patients undergoing total colectomy is given in Table IV also. One death occurred in this group from peritonitis secondary to ileal perforation.

CASE 9. This patient was a man, 40 years old; he gave a history of having had chronic ulcerative colitis for 5 years. The colitis had become progressively worse and anal fistulas had developed. Total colectomy was performed with establishment of a single-barrel ileac stoma. The patient did well postoperatively, was able to eat, and the ileac stoma functioned satisfactorily. Two weeks after operation some obstruction with cramps developed with decrease in return from the ileac stoma, but the obstruction decreased in a few days during which intubation was carried out and fluids were given parenterally. Five weeks after operation right-sided abdominal pain and signs of peritonitis developed suddenly. An exploratory operation disclosed perforation of the terminal ileum about 6 inches proximal to the ileac stoma, with evidence of infarction and impending gangrene. The terminal 18 inches of ileum was resected and the ileac stoma was revised. The patient's condition did not improve, and he died 24 hours later. Necropsy was not obtained.

Colostomy was performed in most cases as a palliative procedure for inoperable carcinoma. None of the patients had complete intestinal obstruction. Pulmonary embolism was the one major complication in this group (Table V) and it was associated with the death of the patient.

TABLE VI.—COMPLICATIONS AFTER MISCELLANEOUS OPERATIVE PROCEDURES

	Chlortetracycline by mouth		*Oxytetracycline by mouth*		*Penicillin-dihydrostreptomycin parenterally*	
	Total cases	*Complications*	*Total cases*	*Complications*	*Total cases*	*Complications*
Resection of small bowel	2	0	2	0	7	0
Colotomy	5	0	1	0	13	3*
Ileocolostomy or colocolostomy	3	0	0	0	5	1*
Ileostomy	2	0	0	0	2	1†
Hartmann's procedure	0	0	0	0	1	0
Total	12	0	3	0	28	5
Deaths		0		0		0

*Wound infection.
†Thrombophlebitis.

CASE 10. A 71 year old man had palliative loop sigmoidal colostomy for extensive carcinoma of the rectosigmoid. He had transitory cyanosis while being placed on the operating table but this was associated with no other symptoms and cleared readily. The patient died as the operative procedure was terminated. Necropsy revealed massive bilateral pulmonary embolism.

The complications in patients undergoing closure of a colonic stoma after preparation with chlortetracycline, oxytetracycline, or penicillin, streptomycin, and dihydrostreptomycin are compared in Table V. All 5 (minor) complications occurred in the last group.

Other operative procedures are considered together in Table VI. The 5 minor complications all occurred in the group of penicillin-dihydrostreptomycin treated patients.

The whole group. The incidence of complications, particularly those of a serious nature, for various types of operative procedures (Tables II to VI) did not vary greatly whether the patients were prepared with chlortetracycline or oxytetracycline given by mouth or with parenterally administered penicillin, streptomycin, and dihydrostreptomycin. Exceptions are seen

TABLE VII.—SUMMARY OF COMPLICATIONS

	Chlortetracycline by mouth		*Oxytetracycline by mouth*		*Total receiving tetracycline*		*Penicillin-dihydrostreptomycin parenterally*	
	No.	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
Total cases	135		108		243		261	
Minor complications	15	11.1	18	16.7	33	13.6	47	18
Wound infection	1		4				19	
Fever of undetermined origin	10		8				8	
Fecal fistula	0		3				12	
Phlebitis	4		3				8	
Major complications	1	0.7	7	6.5	8	3.3	11	4.2
Enterocolitis			1					
Peritonitis							4	
Sigmoidocutaneous fistula			1					
Psoas abscess on right							1	
Subdiaphragmatic abscess							1	
Pelvic abscess							1	
Deep wound infection							1	
Pneumonia			2				1	
Pulmonary embolus	1		3				2	
Total complications	16		25		41	16.9	58	22.2
Deaths	1	0.7	4	3.7	5	2.1	5	1.9

in Table II in which an unusually large number of fecal fistulas occurred after anterior resection in the penicillin-dihydrostreptomycin group and in Table III in which wound infections and other serious infections were more prominent after resection of the colon in the penicillin-dihydrostreptomycin group.

The complications for the entire series are summarized in Table VII. The incidence of minor complications was 4.4 per cent greater, and the incidence of major complications was 0.9 per cent greater in the penicillin-dihydrostreptomycin group as opposed to the tetracycline group. There were 5 deaths in each group.

Of the minor complications, wound infection occurred about three times as commonly in patients receiving only parenterally administered penicillin, streptomycin, and dihydrostreptomycin before operation as opposed to those receiving tetracycline drugs by mouth preoperatively. Of the major complications, peritonitis and other major infections were more frequent in the penicillin-dihydrostreptomycin group. Fever of undetermined origin occurred twice as commonly among patients receiving the tetracycline derivatives by mouth. Micrococcic enteritis did not occur among patients who received only parenterally administered penicillin, streptomycin, and dihydrostreptomycin prior and subsequent to operation on the intestine.

Intraperitoneal intestinal anastomosis. In Table VIII all the operations performed are classed into two groups according to whether or not an intraperitoneal intestinal anastomosis was performed. In operations not involving an intraperitoneal intestinal anastomosis, and in which under ordinary circumstances there would be no contamination of the peritoneal cavity, the incidence of complications was the same whether antibiotics were administered orally or parenterally (22.5 per cent versus 22.2 per cent). However, with operations involving an intestinal anastomosis, the incidence of complications of all types was 13.6 per cent for patients receiving antibiotics by mouth versus 22.2 per cent for patients receiving only penicillin, streptomycin, and dihydrostreptomycin by parenteral injection.

Since a majority of the fecal fistulas, wound infections, and major infectious complications such as peritonitis occurred among patients receiving only parenterally administered penicillin, streptomycin, and dihydrostreptomycin and whose operation involved an intraperitoneal intestinal anastomosis, it seems that the administration of the tetracycline derivatives by mouth before operation may have offered some

TABLE VIII.—OPERATIONS WITH AND WITHOUT INTRAPERITONEAL INTESTINAL ANASTOMOSIS

Operation	*Tetracycline by mouth*				*Parenterally given penicillin and dihydrostreptomycin*	
	Chlortetracycline		*Oxytetracycline*			
	Cases	*Complications*	*Cases*	*Complications*	*Cases*	*Complications*
OPERATIONS INVOLVING INTRAPERITONEAL INTESTINAL ANASTOMOSIS						
Anterior resection	38	5	31	8	76	17
Hemicolectomy	27	3	22	3	69	15
Subtotal colectomy	10	2	4	0	9	1
Closure of colonic stoma	7	0	2	0	10	5
Miscellaneous	10	0	3	0	25	4
Total	92	10	62	11	189	42
Total complications, per cent		21		13.6		42 22.2
OPERATIONS NOT INVOLVING INTRAPERITONEAL INTESTINAL ANASTOMOSIS						
Combined abdominoperineal resection	15	1	15	6	21	1
With endo-anal (pull-through) anastomosis	19	4	22	4	27	9
Total colectomy	3	0	6	2	8	4
Colostomy	4	1	3	2	13	1
Miscellaneous	2	0	0	0	3	1
Total	43	6	46	14	72	16
Total complications, per cent		20		22.5		16 22.2

measure of protection against such complications in those patients.

COMMENT

These data illustrate that, with modern methods of managing patients with various types of surgical intestinal lesions, it is not absolutely necessary to alter the flora of the intestines with antibiotics. The addition of a 3 day preparation of the intestine with orally administered tetracycline[1] prior to operation produced no fewer complications than the simple parenteral administration of penicillin, streptomycin, and dihydrostreptomycin the evening before and subsequent to operation in those patients whose operation did not require an intestinal anastomosis. Of the patients having intestinal operations involving intraperitoneal intestinal anastomoses, the group prepared with tetracycline drugs given orally had fewer complications. The difference was not great, however, and its significance is difficult to determine on the basis of this one particular series.

We hope that in the future other investigators will also institute similar studies upon patients to assist in determining the necessity, as well as the desirability, of altering the intestinal flora with antibiotics in patients who are to undergo operations upon the intestine.

[1]Preoperative preparation with tetracycline derivatives alone is no longer used at this institution. When antibiotic preparation of the bowel is desired before operation, we now use the tetracycline drugs in combination with neomycin.

SUMMARY

The incidence of postoperative complications in a consecutive unselected series of 261 patients who had various types of intestinal operations after parenteral administration of penicillin, streptomycin, and dihydrostreptomycin only is compared with that in a series of 243 patients who underwent various intestinal operations after oral administration of members of the tetracycline group of antibiotics.

The incidence of postoperative complications differed little (5.3 per cent) between the two groups, and there was no significant difference in the mortality rate.

Preoperative preparation of the intestinal tract with orally administered tetracycline drugs produced no fewer complications in those patients whose intestinal surgery did not involve an intraperitoneal intestinal anastomosis than did simple parenteral administration of penicillin, streptomycin, and dihydrostreptomycin the evening before surgery was to be performed and subsequent to operation.

However, preparation of the bowel with tetracycline drugs given by mouth, when intraperitoneal intestinal anastomosis was in-

cluded in the operation, resulted in fewer complications than did preparation with penicillin, streptomycin, and dihydrostreptomycin.

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THE SOURCES OF UPPER GASTROINTESTINAL BLEEDING IN PATIENTS WITH CIRRHOSIS

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THE INTEREST in upper gastrointestinal bleeding in patients with cirrhosis seems to have increased in the past decade, as attested by the numerous publications appearing in the recent medical literature. That patients with cirrhosis frequently bleed from lesions other than esophageal varices has been noted by many. This fact leads to difficulty in the handling of acute bleeding in these patients, for the management of bleeding from esophageal varices differs considerably from the management of bleeding from lesions within the stomach and duodenum. If a surgical attack is proposed, even the placement of the incision (thoracic or abdominal) is a major consideration. Linton and Ellis, Crile, and Phemister and Humphreys have championed a transthoracic approach to the lower esophagus for controlling bleeding presumed to be from varices. Cohn and Mathewson, noting the high incidence of bleeding from lesions related to acid-peptic disease in patients with cirrhosis, have favored an abdominal approach which permits dealing adequately with any intra-abdominal disease, and in addition provides rather ready access to the lowermost several inches of the esophagus. Varices in the distal portion of the esophagus can then be ligated. Baronofsky and Wangensteen have shown that clinically, and in the experimental animal, portal hypertension abets the ulcer diathesis, and therefore results in an increased incidence of acid-peptic lesions within the esophagus, stomach, and duodenum. It has been pointed out by both of these authors that resectional surgery for the treatment of bleeding lesions in the presence of portal hypertension must be considerably more extensive than resectional surgery for bleeding acid-peptic lesions in patients with normal portal tension.

Our interest in this problem has been stimulated by a study, currently being pursued in our hospital, dealing with the management of acute massive upper gastrointestinal bleeding in patients in whom varices are presumably excluded (6). We have attempted to identify liver disease, and therefore to exclude patients with same, by the application of one of the more sensitive liver function tests (bromsulphalein retention), but have found this test to be unsatisfactory; many severely bleeding patients, with subsequently proved normal livers, reveal markedly elevated bromsulphalein retention during an acute episode, only to reveal normal retention after normovolemia has been restored. Emergency roentgenograms, using barium swallow, have proved to be fairly accurate, but far from infallible, in determining whether the acutely bleeding patient is suffering from ruptured varices or from ulcers or other acid-peptic lesions within the lower esophagus, the stomach, or duodenum.

In order to determine if patients with cirrhosis do indeed exhibit more peptic ulcers, and other lesions related to the ulcer diathesis, it was elected to make a study on necropsy material to compare the incidence of acid-peptic lesions in patients dying with cirrhosis with the incidence of similar lesions in patients with essentially normal livers.

MATERIAL

All autopsy protocols at the Kings County Hospital Center, Brooklyn, for the years 1950 through 1955 were reviewed. The

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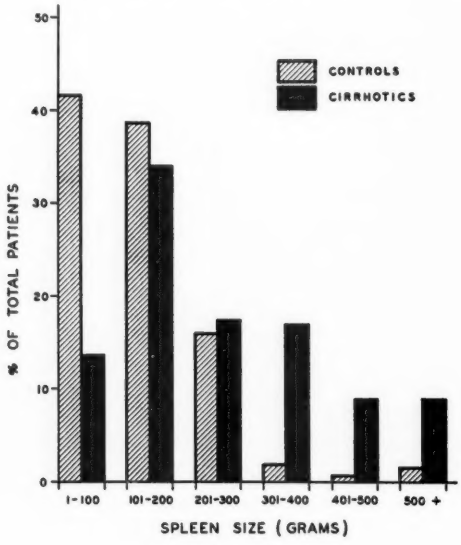

FIG. 1. Spleen size.

charts of all patients with a diagnosis of cirrhosis were thoroughly studied; included were patients in whom the cirrhosis was not the primary cause of death. During the 6 years covered by this study, 6,829 autopsies were performed and in 521 (7.6 per cent) of these, cirrhosis was found and recorded. The protocols of these 521 patients were then individually studied and the following data extracted: age, sex, liver size, spleen size, presence or absence of jaundice, presence or absence of ascites, presence or absence of varices, and a careful tabulation of the presence or absence of ulcers, erosions, hyperemia, congestion, petechiae, and inflammation in the gastrointestinal tract, from the esophagus to the rectum. In addition, the protocols of 1,000 adult patients 20 years of age and over with essentially normal livers were carefully studied and the same information was extracted; these autopsies were performed consecutively in the years 1952 and 1953. These 1,000 cases then served as a control group for comparisons with the patients with cirrhosis.

In making various evaluations and comparisons, spleen size was used as a criterion of portal hypertension. Whether spleen size at autopsy correlates well with actual degree of portal hypertension during life is unknown. No specific information in this regard could be found. Lichtmann indicates that the spleens of patients dying with cirrhosis average twice the size of spleens of patients with normal livers. Since it is known

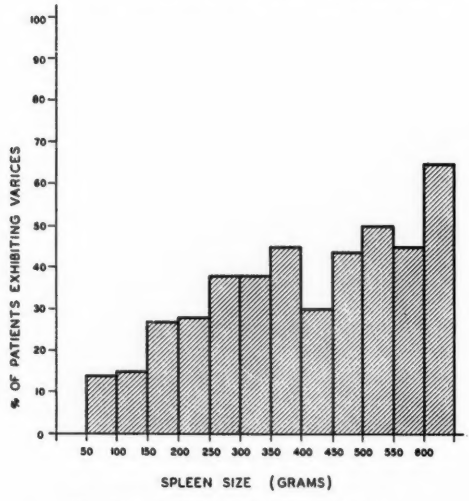

FIG. 2. Relation of varices to spleen size.

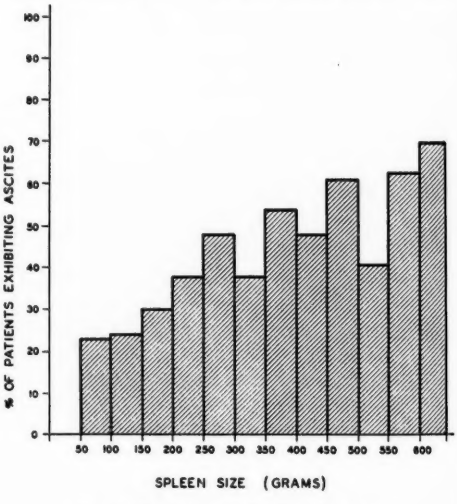

FIG. 3. Relation of ascites to spleen size.

that splenomegaly is very common in cirrhosis and that it is very likely related to the portal hypertension, we have chosen to use the degree of splenic enlargement as an indication of the degree of portal hypertension. This is an assumption; we have no way of knowing if it is entirely valid.

RESULTS

Of the 521 patients with a diagnosis of cirrhosis, 21 were found to have cardiac cirrhosis and 24 to have obstructive biliary cirrhosis. These 45 cases, therefore, were excluded from further consideration in this study. The results reported pertain to the 476 patients with a diagnosis of nutritional (portal, Laennec's) and postnecrotic cirrhosis.

Of the 476 patients, 315 were male and 161 female, giving a male-female ratio of about 2 to 1. The sex ratio in the group of 1,000 control patients is 1.6 males to 1 female. This substantiates the commonly held view that cirrhosis is a more common disease in males. It is interesting to note that the male-female ratio in young cirrhotics less than 41 years of age is only .6 to 1. The recent report of Bearn, Kunkel, and Slater emphasizes the frequency of cirrhosis in young females as compared to young males; apparently alcoholism and poor nutrition did not play a role in the etiology of the cirrhosis. The description of the livers in these young females would indicate that their cirrhosis microscopically is the same as the cirrhosis found in patients of the older age groups.

The age distribution of the 476 cirrhotic patients and the 1,000 control patients is shown in Table I. One might assume from this table that cirrhosis leads to early death, for the majority of the patients with cirrhosis died between the ages of 41 and 70

TABLE I.—DISTRIBUTION BY AGE GROUPS OF CIRRHOTIC AND CONTROL PATIENTS

Age, years	*Patients with cirrhosis, per cent*	*Patients without cirrhosis, per cent*
Less than 31	0.2	9.0
31–40	7.5	8.6
41–50	21.1	10.0
51–60	25.7	15.2
61–70	26.3	24.7
71–80	14.2	23.3
Over 80	4.0	9.0

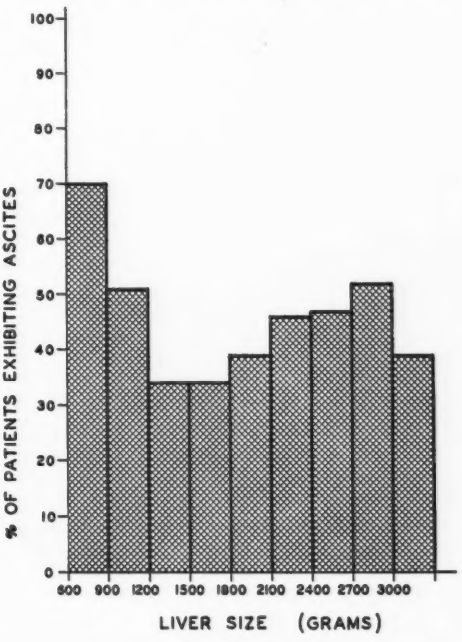

FIG. 4. Relation of ascites to liver size.

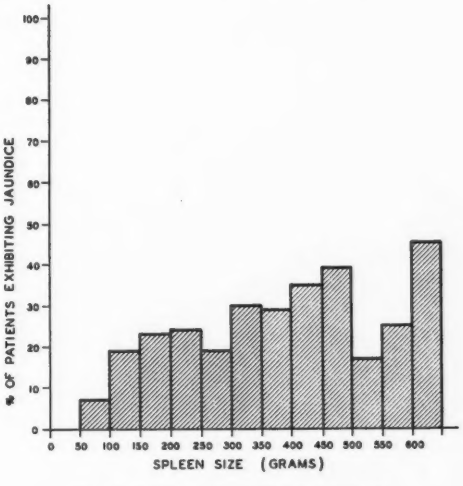

FIG. 5. Relation of jaundice to spleen size.

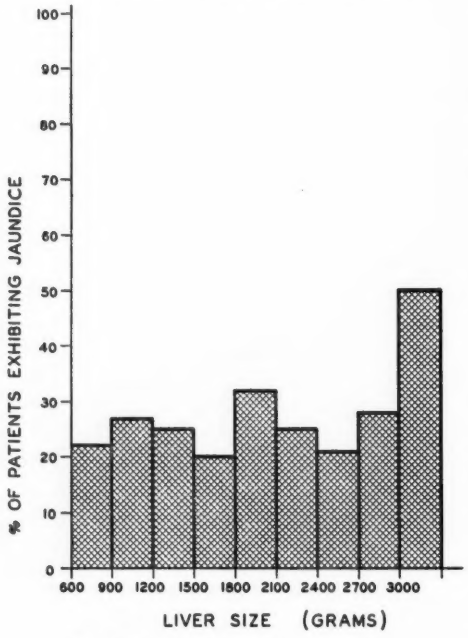

FIG. 6. Relation of jaundice to liver size.

years, whereas proportionately more patients with normal livers lived to older ages. The relatively high number of deaths in patients under 30 years of age with normal livers can be attributed to the large number of accidental deaths in this age group.

The size of the spleens of the 453 cirrhotic patients in whom spleen size was recorded is compared with the size of the spleens in the control group in Figure 1. The expected increased incidence of splenomegaly in the cirrhotic group is borne out here. The average size of the spleen in the cirrhotic group is 244 grams, whereas the average size of the spleen in the control group is 146 grams. These figures compare well with those previously reported by Nissen.

It is probably true that the presence of esophageal varices is well correlated with the degree of portal hypertension. Usually, varices are present only when some degree of portal hypertension exists, and many clinical decisions depend on this knowledge. Using this assumption, an attempt was made to correlate the size of the spleen in the patients with cirrhosis with the presence or absence of esophageal varices (Fig. 2). The correlation is good. The correlation between spleen size and the presence of ascites also is good (Fig. 3). This fact suggests that portal hypertension does indeed play a role in the pathogenesis of ascites in patients with cirrhosis. There is no good correlation between liver size in the patients with cirrhosis and the presence or absence of ascites (Fig. 4). Also, in cirrhotic patients, there appears to be no good correlation between the presence of jaundice and the size of the spleen (Fig. 5), and between the presence of jaundice and the size of the liver (Fig. 6). One hundred and seventy (35.7 per cent) of the patients with cirrhosis showed significant ascites at autopsy. One hundred and ten (23 per cent) showed detectable jaundice at autopsy. These figures compare well with those reported by Nissen, who found ascites and jaundice in 37 and 27 per cent respectively, in an autopsy series.

The total incidence of gastrointestinal findings which may bear some relation to hemorrhage is shown in Table II. The increased incidence of these lesions in the patients with cirrhosis is obvious.

The information which seems of particular importance in this study is the incidence of the various gastrointestinal findings in relation to the degree of portal hypertension (Table III). The data would indicate that portal hypertension per se is not the only factor in cirrhosis responsible for the pathogenesis of these findings. However, if one considers a spleen of larger than 200 grams as evidence of splenomegaly, there seems to be a higher incidence of gastrointestinal disease in the patients with splenomegaly than in the patients with cirrhosis without splenomegaly.

How important these findings will prove to be can best be found by a documentation of the frequency of such gastrointestinal lesions in patients with cirrhosis dying of hemorrhage. The source of bleeding in the

TABLE II.—PERCENTAGE OF PATIENTS SHOWING GASTROINTESTINAL DISEASE AT AUTOPSY

Site	*Pathology*	*Control patients, per cent*	*Cirrhotic patients, per cent*
Esophagus	Congestion*	0.9	1.0
	Esophagitis	1.3	5.1
	Ulcer	0.6	4.4
	Varices	0.1	29.0
Stomach	Congestion*	4.9	15.3
	Gastritis	0.6	6.3
	Acute ulcer (erosions)	1.6	4.2
	Chronic ulcer	1.2	4.6
Duodenum	Congestion*	0.0	2.3
	Duodenitis	0.0	0.4
	Acute ulcer	0.5	1.5
	Chronic ulcer	0.7	2.1
Jejunum and ileum	Congestion*	1.9	7.3
	Enteritis	0.2	0.8
	Ulcer	0.0	0.4
	Marginal ulcer	0.1	0.2
Colon and rectum	Congestion*	0.3	5.5
	Ulcer	0.9	1.6
	Colitis	1.7	2.1

*Congestion is used here to include: diffuse hyperemia, multiple petechiae, diffuse petechial hemorrhages, and congestion. These were the terms used by different pathologists to describe what we consider to be the same change.

TABLE III.—PERCENTAGE OF CIRRHOTIC PATIENTS SHOWING GASTROINTESTINAL DISEASE, ACCORDING TO THE PRESENCE OR ABSENCE OF SPLENOMEGALY

Site	*Pathology*	*Patients with spleens 200 grams or less, per cent*	*Patients with spleens larger than 200 grams, per cent*
Esophagus	Congestion*	0.9	1.3
	Esophagitis	6.4	4.7
	Ulcer	1.8	7.1
	Varices	21.0	40.1
Stomach	Congestion*	14.1	18.0
	Gastritis	4.5	8.6
	Acute ulcer (erosions)	4.5	4.3
	Chronic ulcer	3.6	6.4
Duodenum	Congestion*	1.8	3.0
	Duodenitis	0.4	0.4
	Acute ulcer	0.9	2.1
	Chronic ulcer	2.3	5.5
Jejunum and ileum	Congestion*	4.5	10.7
	Enteritis	0.9	0.8
	Ulcer	0.4	0.4
	Marginal ulcer	0.0	0.4
Colon and rectum	Congestion*	3.6	7.5
	Ulcer	3.2	0.4
	Colitis	0.9	5.1

*Congestion is used here to include: diffuse hyperemia, multiple petechiae, diffuse petechial hemorrhages, and congestion. These were the terms used by different pathologists to describe what we consider to be the same change.

85 cirrhosis patients in whom hemorrhage contributed to death was definitely from varices in 38 patients, from varices or another lesion in 18, and definitely from another lesion in 29. In Table IV are listed the lesions, other than esophageal varices, causing bleeding which contributed to death. It is important to note that the most common lesion giving rise to extravariceal bleeding in these cirrhotic patients is hemorrhagic gastritis. The frequency of this lesion as a cause of upper gastrointestinal bleeding has also been noted by Palmer and emphasized by Dagradi and associates. Not as well known, but even more provocative is the finding of severe bleeding, contributing to death, arising in the colon in 4 of the 47 cirrhotic patients who died with major hemorrhage.

TABLE IV.—LESIONS (OTHER THAN ESOPHAGEAL VARICES) CAUSING BLEEDING WHICH CONTRIBUTED TO DEATH

Lesion	*No. of patients*
Hemorrhagic gastritis	16
Gastric ulcer (chronic)	9
Duodenal ulcer (chronic)	6
Acute gastric ulcers (erosions)	3
Esophagitis and gastritis	2
Acute enterocolitis	2
Acute colitis	2
Site undetermined	7
	47

In Tables II and III it is apparent that congestion of the colon is much more frequent in patients dying with cirrhosis than it is in patients dying with essentially normal livers, and that both congestion and colitis are more frequently found in cirrhotic patients with portal hypertension (splenomegaly) than in those without such hypertension. Whether colonic congestion plays a role in the pathogenesis of colitis which leads to severe hemorrhage can only be conjectured. The absence of severe hemorrhage originating in the mesenteric small intestine is also noteworthy. Detectable congestion is much more common in this segment at autopsy in cirrhotic patients than in noncirrhotic patients, and also appears to be more common in cirrhotic patients when portal hypertension is present (Tables II and III).

SUMMARY

1. A review of autopsies performed in 476 cirrhotic patients and 1,000 control patients during the same time period revealed different sex ratios and age distributions in the two groups.

2. If spleen size at autopsy is an indication of the degree of portal hypertension existent during life, there is good correlation between the incidence of varices and ascites and the degree of portal hypertension. No such correlation was found to exist between the incidence of varices and ascites and the size of the liver. Also, no such correlation was found to exist between the size of the spleen and the presence of jaundice.

3. Upper gastrointestinal lesions which commonly serve as sources of hemorrhage are found more frequently at autopsy in cirrhotic patients than in those with normal livers. These lesions are found more frequently in cirrhotic patients with splenomegaly than in cirrhotic patients without splenomegaly.

4. In 34 per cent of cirrhotic patients dying with hemorrhage, the source of bleeding was not from varices; in 21 per cent a lesion was present which could as well have been the source of hemorrhage as the varices; in only 45 per cent of these patients did the bleeding quite surely originate in esophageal varices.

5. Most of the extravariceal sources of bleeding in cirrhotic patients are found in the stomach. Hemorrhagic gastritis is the most frequent source of such bleeding.

6. The colon is frequently, and the mesenteric small intestine rarely, the site of major hemorrhage which contributes to death in patients with cirrhosis.

CONCLUSIONS

1. Sources of bleeding other than varices must be considered in dealing with the cirrhotic patient presenting with upper gastrointestinal hemorrhage.

2. Because of this fact an abdominal approach to the stomach and lower esophagus seems appropriate for operative control of such hemorrhage.

3. Empiric subtotal gastrectomy should be done in those patients with severe upper gastrointestinal bleeding in whom bleeding from varices is not demonstrated.

4. One must not ignore the lower gastrointestinal tract as the site of alimentary tract hemorrhage in cirrhotic patients.

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THE SURGICAL APPLICATION OF FREEZE-DRIED HOMOLOGOUS DURA MATER

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REPLACEMENT AND REPAIR of dural defects remains a challenge to the surgeon. Various naturally occurring substitutes in the form of fresh autogenous sheets of fascia, split dura mater, and pericranium have been helpful. Synthetic membranes or films of polyethylene, fibrin, and gelatin have found application. These and other replacement materials have been found wanting in one or more of various qualities needed for widespread, sustained use: (1) The source of the substituting membrane may limit the size of the defect which can be covered; (2) the membrane may be too fragile to handle and will hold sutures poorly; (3) its source may require a second operative site preparation; (4) it may not adapt itself to watertight closure, and its physical properties may be unsuitable to covering an exposed surface of the brain or spinal cord; and (5) it may evoke an unwanted reaction and cicatrix with the brain. In brief, the best material for the reconstitution of dural integrity is dura mater. In this article is presented the surgical experience with the application of freeze-dried homologous dura mater to 16 patients for the repair of tissue defects.

In 1947 Hufnagel (2) reported the feasibility and efficacy of utilizing rapidly frozen arterial segments in tissue transplantation. Marrangoni and Cecchini in 1950 applied the freeze-drying technique to the method of preservation of such tissues.

Sewell and Koth (5, 6,), in 1954, reported upon the experimental use of dura mater prepared by the method of Marrangoni and Cecchini. In 1957, Campbell, Bassett, and Robertson recorded their experience with applications of vacuum-stored dura mater obtained aseptically and presented their data of follow-up "second look" examinations of such implanted specimens.

In 1953, Hufnagel, Rabil, and Reed (3) reported the value of ethylene oxide as a sterilizing agent (used prior to freeze-drying of the tissue), thereby precluding the need for removing the dura mater from the donor (fresh autopsy material) under aseptic conditions. The grafts utilized in the present case material were prepared in accordance with this latter principle.

METHOD

Beginning in February 1956, specimens of fresh human autopsy dura mater have been prepared for anticipated neurosurgical needs. The tissue is taken at routine autopsy examination under unsterile conditions, placed in a saline solution, to which is added both aqueous penicillin and streptomycin. After trimming to desired shapes and sizes, the tissues are sterilized by immersion in ethylene oxide for 30 minutes. Quick freezing is accomplished with carbon dioxide ice and 95 per cent ethyl alcohol in 10 minutes, following which the specimens may be stored (at −70 degrees C.) until sufficient numbers are available to justify operating the freeze-dryer. The final step is completed by removing all moisture in a vacuum of 0.3 to 0.4 micron for 24 hours. The dura mater is then sealed in glass tubes ready for storage. Room temperature storage of the "banked" dura mater has been our custom. The tissue is reconstituted at the operating table by its removal from the sealed container under sterile precautions

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and immersion in physiologic salt solution or distilled water for 20 to 30 minutes. In this state it is ready for use; it is tough, pliable, and easily handled, a bit more chalky in color and a bit more leathery or "chamoislike" but otherwise physically similar to normal dura mater in its surgical properties.

MATERIAL

On April 5, 1956, two months after the preparation of the first specimen for storage, the first graft was implanted for repair of a dural defect produced by the total excision of a parasagittal, psammomatous meningioma. At the time of writing 16 patients have received dural grafts varying in size from 16 to 96 square centimeters in area. These applications have been made by the members of the faculty and resident staff of the neurosurgical service, University of California Medical Center, Los Angeles. The grafts have lent themselves to various uses:

1. Replacement of dura mater excised with and for meningioma surgery—6 cases. Defects over the base of the anterior fossa and over the frontal poles were suitably repaired with the grafts, as were defects over the cerebral convexities and along the superior longitudinal sinus. Varying suture techniques were employed; the optimal seemed to be the use of through-and-through mattress sutures over imbricated edges with the graft lying beneath the host dural margins. The exception to this would be fixation of the graft along the longitudinal sinus where, of necessity, suture may be restricted.

2. Replacement of dura mater over the orbit—1 case. In this location the graft provided a watertight coverage of the frontal pole and acted as a sling to the brain tissue over defects in the orbital roof. Its use was compatible with exenteration of the orbit in the presence of bony excision of the orbital roof.

3. Adjunctive use for decompressive purposes—3 cases. The graft material permitted closure of dural margins over excessively tight brain tissue and protected the latter from fracture and cicatrix formation. It was adaptable to the spinal theca and effected a watertight repair of a posttraumatic dural defect in the thoracic region.

4. Miscellaneous intracranial uses—4 cases. Application has been made of the membrane for tight closure of cerebrospinal fluid in cases of postoperative pseudomeningoceles. It was also satisfactory in repairing old dural defects attendant upon operation for posttraumatic epilepsy.

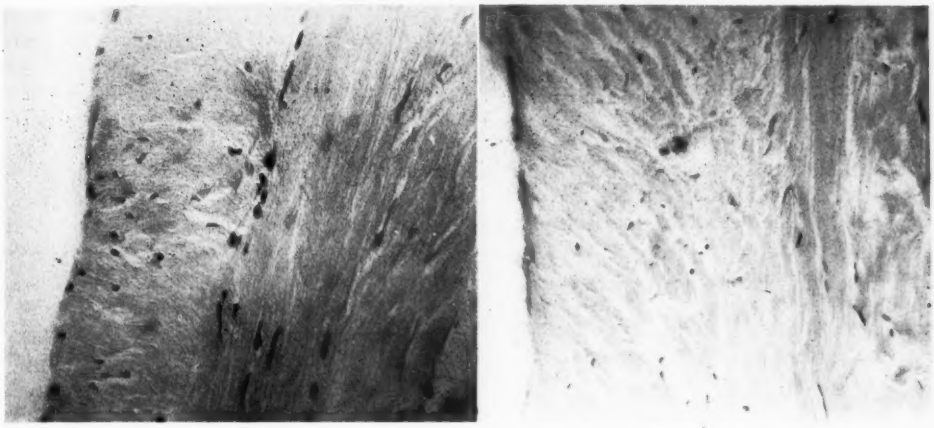
5. Extracranial applications—2 cases. Use has been made of the prepared tissue to repair facial defects in the temporal fossa and by a colleague in general surgery (Donald Mulder) to produce a relatively airtight closure in the thoracic wall.

RESULTS

Among the first 15 patients no reactions have been witnessed that might be attributed to the grafts. The first patient continues to suffer focal seizures from her meningioma site, but, since these episodes had been present for 25 years prior to operation and since their incidence and nature have not changed (except to improve), it is not believed that they incriminate the graft implantation. The sixteenth patient presented himself with infected cerebral tissue that fungated through a necrotic scalp in association with a malignant glioma. A dural repair was performed with the graft material, but at the present time the wound continues to be infected.

Cultures of the graft tissue taken at the time of implantation are available from 7 patients; 6 cultures were sterile. The seventh grew a coagulase negative micrococcus; however, no trouble occurred within the patient's wound.

Comparison of histologic preparation of fresh autopsy dura mater and dura mater of the same source sterilized and freeze-dried by the methods described demonstrates some decrease in cellularity and a tendency to separation of the collagen layers of the latter tissue (Fig. 1a and b).



a b

FIG. 1. Comparison of normal dura mater and freeze-dried dura mater from same autopsy specimen. a, Normal dura mater. Hematoxylin and eosin, ×189. b, Freeze-dried dura mater reconstituted in distilled water and prepared by standard histologic technique as in "a." Hematoxylin and eosin, ×189.

In Case 12, autopsy material secured on the eighth postoperative day revealed no adhesive reaction between graft and host brain. Histologic study demonstrated a distinct line of separation between the two tissue segments, acellularity of the donor tissue, and a mild cellular reaction on the brain surface of the suture line. Erythrocytes could be seen, however, within channels of the graft tissue, but the latter did not appear viable.

In Case 5, a second stage procedure permitted examination of the reaction of the graft and host tissue at this time, 4 months following implantation. The dural graft was more pale and ivory-colored than the host dura mater. The graft showed a smooth inner surface and was securely incorporated into the margins of the host dura mater. There were easily lysed adhesions of comparable degree, between the host dura mater and the pia-arachnoid and between the graft dura mater and the pia-arachnoid. The excess dural graft tissue, which had been implanted to permit expansion, if needed, had formed a firm fold at its attachment to the host tissue. The latter had calcified and ossified, whereas the graft tissue had not.

Histologic examination of the suture line revealed a syncytium of thick, trabeculated intradural bone in the host dura, and remnants of the silk suture material could be identified. The graft dura was vascularized with sparsely placed capillaries containing blood. It appeared viable. There was an incomplete break in continuity at the junction of the host and graft dura. On the inner aspect (pial side) of both host and graft dura, a coagulum mixed with fresh blood blended with structures of a more fibrillar nature, possibly representing, in part, degenerated collagen of the inner layer of the host and graft dura mater.

DISCUSSION

Histologic study of the experimental animal dural graft preparations by Sewell and associates (1954 to 1955) demonstrated that invading fibroblasts replace the cells of the graft by laying down new collagen. Some slight adhesions were noted between their experimental grafts and the pia-arachnoid. No change in properties occurred, and they observed no shrinkage of the graft.

The homologous tissue is superior to known synthetic products and to autologous grafts because it covers defects with a mem-

brane whose properties approximate those of the host tissue more closely than any other known. Since the graft need only serve a mechanical purpose, there is no need for metabolic activity or survival of the graft cells. As a consequence, these banked sheets of dura mater are admirably suited by their physical properties for the needs described. Invasion by host mesodermal tissue and permanent replacement by the host of the graft skeleton seems to be the ultimate fate of these membranes. Whether the center of the largest grafts can be vascularized before necrosis occurs is as yet unanswered.

SUMMARY AND CONCLUSIONS

Since April, 1956, sterilized and freeze-dried homologous dura mater has been used in 16 patients who required repair of defects in the dura mater or fascia. It is admirably suited for storage in sealed ampules at room temperature and is readily available for surgical application after brief reconstitution in water or saline at the operating table. In the first 15 patients no untoward reactions attended its use. In the last patient, with an infected cerebral fungus, wound suppuration continues. Watertight, tough, pliable dural replacements for defects of sizes up to 96 centimeters square have been successfully accomplished. This form of graft material appears superior to any other dural replacement, synthetic or otherwise, currently available.

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SINUS HISTIOCYTOSIS OF LYMPH NODES IN CANCER

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FOR THE PAST 5 YEARS we have been investigating the relationship between the survival of cancer patients and various structural features of their primary cancers and regional lymph nodes (3–10). The lymph node features which were studied included follicular prominence, sinusoidal structure, and the cellular pattern of the pulp. Cancer patients with a marked degree of sinus histiocytosis (SH) of the regional lymph nodes were found to have prolonged survivals. It was also observed that a greater degree of sinus histiocytosis was present in the regional lymph nodes of breast and gastric cancer patients with long postoperative survival than in those of unselected patients with breast and gastric carcinoma. Conversely, sinus histiocytosis was uncommon among breast and gastric cancer patients who died postoperatively of the disease within 3 years. These data suggested to us that sinus histiocytosis was a structural feature of prognostic significance which reflected a host reaction to the tumor.

More recently Berg has studied sinus histiocytosis in the axillary lymph nodes of breast cancer patients. He examined a mean of 11 nodes per case and used the average value of all the nodes for his evaluation of the degree of sinus histiocytosis in individual cases. These average values were then considered in relation to survival 3 years postoperatively. He agreed that, "the group of patients without axillary metastases will show more sinus histiocytosis than those with such metastases and also that patients who die within three years after mastectomy will have shown less histiocytosis than those who survived." However, he believed that, "... the observed association of low histiocytosis and poor prognosis is indirect only and dependent upon known prognostic factors, primarily the quantity of axillary metastases at the time of operation." He doubted that sinus histiocytosis "represents a host reaction of any type, meaningful or not." This latter conclusion was based on his assumption that sinus histiocytosis is a normal structural feature of lymph nodes which is effaced by metastases to the nodes, i.e., "At the same time when metastases are limited to level I, levels II and III may be expected to show normal histiocytosis."

Although his article bore the interesting title, "Sinus Histiocytosis: a Fallacious Measure of Host Resistance to Cancer," no data were presented concerning the survival of patients having varying degrees of sinus histiocytosis. However, he did present the mean SH values of the axillary lymph nodes in 36 class I breast cancer patients who were alive and 6 class I breast cancer patients who were dead 3 years postoperatively. Despite the limited number of cases studied, his data did indicate a somewhat higher average degree of histiocytosis for those patients surviving the 3 year postoperative period. At this point he further subdivided his data according to the size of the primary tumors. Such a subdivision of class I cases would seem to be unwarranted, since in 1955 Berg had stated that there was no significant difference in the survival of patients with varying sized tumors when no axillary nodes were involved or if level I only was positive.

Nevertheless, Berg's comments have prompted us to re-examine and extend our data in an attempt to answer, for ourselves, the following questions: (a) Is sinus histiocytosis a normal structural feature of lymph nodes? (b) Is the prognostic significance of sinus histiocytosis dependent upon the pres-

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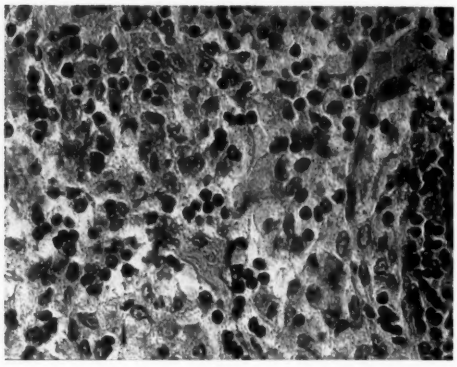

FIG. 1. Lymph node showing sinusoids dilated by large vacuolated histiocytes. Note the distinct cell borders. This is not sinus histiocytosis.

ence or absence of lymph node metastases? (c) Is the prognostic significance of sinus histiocytosis dependent upon the grading of the primary tumor?

We are well aware of the complexity of factors which may affect the biologic behavior of human cancer. Therefore, in this article detailed data are presented from which analyses may readily be made by others and against which our conclusions may be evaluated. We do not hold that sinus histiocytosis is the only factor in determining cancer behavior. However, we do believe that our data indicate it to be an expression of a prognostically significant factor in some types of cancer.

MATERIAL AND METHODS

The sinusoids of lymph nodes may vary markedly in their structural appearance. In many lymph nodes no distinct sinusoids are recognizable or they may be limited to a narrow space between blood vessels and the medullary pulp. In other instances they may be markedly dilated and constitute a major portion of the lymph node. Such dilated sinusoids may be further subdivided in accordance with their cellular content, viz., (a) acellular, edematous sinusoids; (b) sinusoidal catarrh characterized by numerous cells of different types including lymphocytes, plasma cells, large mononuclear cells with and without vacuolization and scattered red cells; (c) sinusoidal "phagocytosis" characterized by proliferations of large rounded mononuclear cells having distinct cell borders. Such sinusoidal phagocytes may have a granular nonvacuolated cytoplasm or may show evidence of extensive erythrophagocytosis, particle phagocytosis (anthracotic hilar nodes), or lipid phagocytosis (lipogranulomatous appearance); (d) syncytial histiocytosis characterized by a proliferation of mononuclear cells having indistinct cell borders, an elongated shape, and a syncytial arrangement in the sinusoids. This sinusoidal pattern may also be further divided into the following subgroups (1) reticular syncytial histiocytosis characterized by a loose arrangement of the elongated cells which are separated by clear fluid filled spaces; (The cytoplasm is typically fibrillar and poorly stained.) (2) erythrohistiocytosis characterized by an elongation of erythrocyte-containing phagocytes and a loss of distinct cell borders; (3) vacuolated histiocytosis, elongated compactly arranged histiocytes having vacuolated cytoplasm and varying degrees of hyalinization of the cytoplasm; (4) sinus histiocytosis characterized by finely granular nonvacuolated eosinophilic cytoplasm, ovoid nuclei and minimal admixture of other cell types; (Typically, such nodes have a lymphocytic pulp and minimal follicular prominence.) (5) sinus hyalinization, replacement of sinusoidal structure by refractile amorphous amyloid-like material; (6) sinus fibrosis, fibroblastic transformation of sinusoids.

TABLE I.—PER CENT INCIDENCE OF SH AMONG LYMPH NODE SAMPLING FROM NONCANCER PATIENTS

Source	*Site*	*No. of cases*	*—SH grade, per cent—* *0–1*	*2*	*3–4*
Surgical					
	Axillary	17	94	6	—
	Others	118	96	2	2
Autopsy					
	Axillary	12	100	—	—
	Others	174	100	—	—
Total					
	Axillary	29	97	3	—
	Others	292	98	1	1

The latter two sinusoidal types sometimes appear to be replacing a pre-existent sinus histiocytosis.

The present report is concerned with sinus histiocytosis as defined before and distinguished from the various other sinusoidal patterns. Throughout this study care has been taken to define the sinusoidal structures as accurately as possible and to avoid confusion with lipogranulomatous change, erythrophagocytosis, and erythrohistiocytosis.

The degree of sinus histiocytosis was evaluated in the following groups of lymph nodes.

Control lymph nodes. This series consisted of lymph nodes removed from noncancer patients. The nodes were obtained from various areas including cervical, axillary, inguinal, intra-abdominal, and mediastinal. These nodes had been removed either for diagnostic purposes or in the course of operative procedures for nonneoplastic disease. In addition, lymph nodes were obtained from autopsy cases.

Lymph nodes draining cancer. This series was composed of the regional lymph nodes removed in the course of resections of various types of cancer. The frequency of sinus histiocytosis in these cases was determined in the entire series and in relation to: (a) the presence or absence of regional node metastases, (b) the survival of the patients, and (c) the grade of the primary tumor.

All the available lymph nodes from an individual case were examined as to the prominence of SH and the case was then graded according to the highest grade found in any node. The number of nodes obtained in the individual cases varied from 1 to 26, with most of the breast cancer cases being represented by a minimum of 8 nodes. In those cases graded 0–1 there was complete uniformity in the SH grade of the nodes. In about 10 per cent of the cancer cases with metastases the lymph node structure was unreadable because of complete replacement by tumor tissue. Such cases were assigned a lymph node reading of 0. When the SH grade was $\geqslant 2$ variability was encountered, viz., only about one-fourth of the nodes had SH grades $\geqslant 2$. In all instances, however, the SH grade assigned to the case was that of the node showing the highest grade.

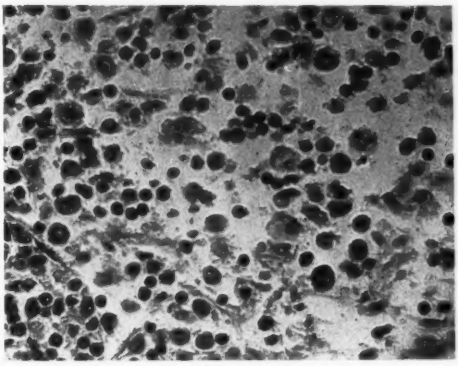

FIG. 2. Lymph node showing sinusoids dilated by proteinaceous fluid containing free floating cells. This is not sinus histiocytosis.

RESULTS

In Table I we have indicated the relative frequency of SH encountered in the lymph nodes of noncancer patients. It will be noted that we have separated the data according to anatomic site and type of sample (surgical or autopsy). It is evident that in none of these control groups was SH other than a

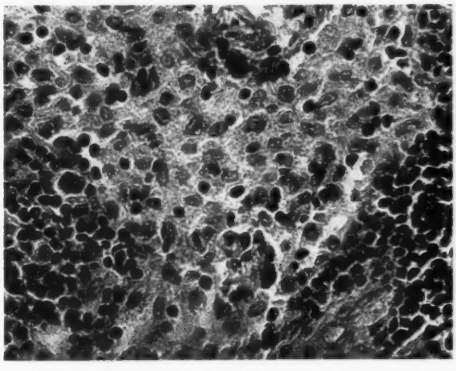

FIG. 3. Lymph node showing sinusoids dilated by a syncytium of histiocytes which have a somewhat fusiform arrangement. This is sinus histiocytosis.

TABLE II.—PER CENT INCIDENCE OF SH GRADES IN REGIONAL LYMPH NODES OF CANCER PATIENTS

		SH grade, per cent		
Group	*No. of cases*	*0–1*	*2*	*3–4*
Total series	1331	76	16	8
Breast	747	66	27	12
Colon	266	99	1	—
Gastric*	63	90	10	—

*Consecutive operable cases.

TABLE III.—PER CENT INCIDENCE OF SH IN CLASS I BREAST CANCER CASES IN RELATION TO SURVIVAL

		SH grade, per cent		
Series	*No. of cases*	*0–1*	*2*	*3–4*
Total series	324	49	33	18
Select series*	29	62	31	7
Dead 3 yrs.	30	63	34	0
Alive 5 yrs.	108	34	39	27

*Consecutive series of cases with average of 20 nodes per case.

TABLE IV.—PER CENT INCIDENCE OF SH IN CLASS II BREAST CANCER CASES IN RELATION TO SURVIVAL

			SH grade, per cent		
Series	*No.*	*U**	*0–1*	*2*	*3–4*
Total series	423	27	53	14	6
Select series†	30	3	70	23	3
Dead 3 yrs.	106	31	61	7	1
Alive 5 yrs.	90	23	39	21	17

*U, lymph nodes unreadable due to overwhelming metastases.
†Consecutive series of cases with average of 20 nodes per case.

relatively rare finding. The data did not indicate that the absence of cancer, primary or metastatic, was associated with SH of lymph nodes from diverse sites.

The paucity of sinus histiocytosis in the lymph nodes in this series was not simply the result of sinus compression by overgrowth of the pulp and follicles since approximately one-fourth of the cases had prominent sinusoids which were either hypocellular or filled with lymphocytes and macrophages (sinus catarrh). The findings in this series of control nodes did not support the thesis that sinus histiocytosis is a common or normal structural feature of lymph nodes of non-cancer patients.

TABLE V.—PER CENT 5 YEAR POSTOPERATIVE SURVIVAL IN RELATION TO SH GRADE AND STAGE

	Class I		Class II	
SH grade	*No.*	*Per cent survival*	*No.*	*Per cent survival*
Total series				
0–1	231	42	262	32
2	56	84	44	52
3–4	36	95	23	83
Breast series				
0–1	65	57	189	28
2	60	70	36	50
3–4	29	97	17	88

The group of lymph nodes draining cancer included the regional lymph nodes from cases of diverse types of cancer. Table II contains the pertinent data concerning the frequency of SH grades in this series. Only one-fourth of the cases were graded $\geqslant 2$ while less than 10 per cent of the cases were graded $\geqslant 3$. Although the cancer series was characterized by a higher frequency of SH than the control series the incidence of SH in the cancer cases was not high.

There were distinct differences in the incidence of SH among the different types of cancer. While the axillary lymph nodes were graded $\geqslant 2$ in approximately one-third of the breast cancer series, SH was rare in the regional lymph nodes removed with colon carcinomas. In the operable gastric cancer series SH was uncommon, but more frequent than in the series of colon cancers. These data fail to support the thesis that SH is a usual structural feature of the regional lymph nodes of cancer patients.

In Tables III and IV is presented the frequency of SH grades of the axillary lymph nodes of breast cancer cases in relation to the absence (class I) or presence (class II) of axillary metastases for the total series of operable breast cancer cases. It is apparent that the incidence of SH $\geqslant 2$ was more than twice as frequent in the class I as in the class II series. However, SH was not a constant feature in the class I cases since approximately 50 per cent of the class I cases had SH grades < 2. Essentially similar values were obtained in a consecutive series of breast cancer cases in which an average of 20 axillary nodes were recovered per case. These findings are inconsistent with the thesis that SH is a usual feature of axillary nodes which are free of metastases. It should also be noted that the presence of lymph node metastases did not rule out the occurrence of SH. Approximately 20 per cent of the class II cases had SH grades $\geqslant 2$. We

have, in fact, encountered SH in lymph nodes containing metastatic carcinoma.

If the prognostic significance of SH was dependent upon the amount of axillary metastases then no difference in the incidence of SH would be expected among class I cases regardless of the survival in such cases since all of these patients are known to be free of such node involvement. In order to test this theory we have compared the frequency of SH grades in those class I patients known to have survived 5 years with those dead of their disease within 3 years postoperatively as well as with the SH grades in the total series of class I breast cancer cases. These data are listed in Table III. Despite the fact that these patients were free of axillary metastases distinct differences in the frequency of SH were found in relation to survival. In the patients surviving 5 years the frequency of SH $\geqslant 2$ was greater than that found in the total series of class I breast cancer patients and in the group dead 3 years postoperatively. Conversely, the frequency of SH $\geqslant 2$ was less in those patients dead 3 years postoperatively than in the total breast series or in the long survival series. These data indicate that the frequency of SH was not critically dependent upon the amount of axillary metastases and that SH was more closely related to the survival of the patient than to the amount of axillary metastases. Table IV demonstrates that the class II patients also exhibited a similar relationship between survival and the incidence of SH.

It should be noted that a similar tendency was found in Berg's data (his Tables 3 and 4), viz., the average values for SH in class I cases were: total class I, 2.00; living 3 years postoperatively, 2.07; dead 3 years postoperatively, 1.95.

In a series of long surviving gastric cancer patients (64 cases) the incidence of SH $\geqslant 2$ was 27 per cent. In contrast, in resectable gastric cancer patients dead of their disease within 3 years postoperatively (82 cases) SH ≥ 2 was found in only 6 per cent (4). However, in colon carcinoma patients SH was not seen in the total, short survival or long survival series.

TABLE VI.—POSTOPERATIVE SURVIVAL IN RELATION TO SH AND N GRADES IN CLASS I BREAST CANCER CASES

	SH grade											
	0–1				2				3–4			
N grade	Dead		Living		Dead		Living		Dead		Living	
0–1	0.5	2.5	5	25	1	4	5		4	5		
	0.8	2.8	5		1.5	10	6		6	5		
	1	3	6		2		9			6		
	1	3	7		2		9			7		
	1	4	9		2		10			7		
	1.5	4	10		2.5		12			7		
	1.8	8	10		3		15			10		
	2		14		3					10		
	2		16		3							
	2		17		3.5							
2	0.8	4.5	6		0.5		5	10	9	5		
	1	5	10		1		5	12		6*		
	2	6.5	12		2.3		5	13		6		
	2	7			2.3		6	16		7		
	2				2.3		6	18		7		
	3				4		6			8		
	3				6		7			9		
	3				8		8			13		
	3.5						9*					
	1.8		5	6	2.5		5	8	18*	18	6	11*
3–4	2		5	7	6.5		5	8			6	14*
	9		5	7	7		5	8			7	
	9		6	8	15		5	8			8	
	10		6	9			6	9			8	
	10		6	10			7	10			9	
	18		6	12			8	17			10	

*Living with disease.

The relationship between SH and survival was also evaluated by determining the per cent 5 year postoperative survival associated with the varying degrees of SH. This relationship was also studied in regard to the presence and absence of regional lymph node metastases. The pertinent data are indicated in Table V. In both the total and the breast cancer series the per cent 5 year survival rose progressively with the increasing grades of SH. In Figure 4 we have plotted the per cent 5 year survivals as found in relation to the SH grades of class I and

TABLE VII.—PER CENT 5 YEAR POSTOPERATIVE SURVIVAL IN CLASS I BREAST CANCER CASES IN RELATION TO SH AND N GRADE

	SH grade					
	0–1		2		3–4	
N grade	No.	Per cent survival	No.	Per cent survival	No.	Per cent survival
0–1	28	41	19	42	10	90
2	16	38	22	73	9	100
3–4	21	90	19	95	10	100

TABLE VIII.—CLASS II BREAST CANCER CASES—POSTOPERATIVE SURVIVAL IN RELATION TO SH AND N GRADES

N grade	*Unreadable*				*SH grade*											
					0–1								*2*		*3–4*	
		D		*L*				*D*				*L*	*D*	*L*	*D*	*L*
0–1	0.5	1	2	6	0.3	1	1.3	2	2	3	4.5	5	1	6	3	5
	0.5	1	2.5	6	0.5	1	1.5	2	2.5	3	5	5	1	11	5	8
	0.5	1.5	2.5		0.5	1	1.5	2	2.8	3.3	5	6	1.3	13		15
	0.5	1.5	3		0.5	1	1.5	2	3	3.5	5	7	2			
	0.5	1.5	3.5		0.5	1	1.5	2	3	4	5.5	8	2			
	0.5	1.5	4.5		0.5	1	1.5	2	3	4	7	8	3			
	0.5	1.5	9		0.5	1	1.5	2	3	4	9		3			
	0.8	1.5	9		0.5	1	1.5	2	3	4	9		4			
	0.8	1.8	11		0.8	1	1.8	2	3	4	9		4.5			
	0.9	2			0.8	1	2	2	3	4	10					
	1	2			0.8	1	2	2	3	4.3						
2	0.3	6		5*	1	2	4					5	2	5*	1	5
	0.3			5	1	2.8	5					5	2.5	8	5	9*
	1			7	1.3	3	5					6	4	10	7	10
	1			8	1.5	3	6					8	4	13	7	
	2			9	1.5	3	6					8	4	14	15	
	2			14	1.8	3.5	7					10	4			
	2.8				2	4						11	4			
	3				2	4						25	8			
	3.5				2	4							11			
	5.5				2	4							12			
3–4	2			5	1.8	6						8	3	5	8	5
	4			6	1.8	7						8	6	6*		6
	6			11	2	9						25	7	6		9
	10			12	2	13							7	9		
	13			15	2	16								10		
					2.5											

*Living with disease.
D, dead; L, living.

class II breast cancers. Since the patients in the class I series are free of axillary metastases the degree of lymph node involvement should not be a factor in their SH-survival relationship. The progressive increase in survival with increasing SH in the class I cases negates the assumption that the relationship is dependent upon the degree of axillary metastases. The curve obtained for the class II cases was similar to that of the class I series but at a lower level.

It will be noted that we have plotted the cases of unreadable nodes (due to overwhelming metastatic involvement) separately from those cases graded 0-1. The percentages of 5 year survival in the class II unreadable, class II 0-1, and class I 0-1 groups were 30, 28, and 57 per cent respectively. The absence of axillary metastases appeared to improve the survival as compared to the groups with metastases. However, there was no appreciable difference between the survivals of the class II 0-1 and the unreadable group despite the fact that the degree of node involvement was 50 per cent in the former and 100 per cent in the latter group. This observation is contrary to the thesis that survival is related in a simple linear fashion to the amount of lymph node involvement. Breast cancer patients having similar SH values had a poorer prognosis when lymph node metastases were present than similar patients without metastases. However, within each of the classes of breast carcinoma a prognostic subdivision existed in relation to the degree of SH.

The prognostic significance of SH persisted even among those breast cancer patients known to have died of their disease. The over-all 5 year survival value for this group (275 cases) was 24 per cent. In 208 of such patients without SH the corresponding value was 17 per cent while in 67 patients with SH ≥ 2 the value was 43 per cent. It

would appear that the prognostic significance of SH is not dependent upon complete surgical eradication of the disease.

In previous studies (5, 8, 10) we had confirmed the findings of Bloom that the survival of breast cancer cases could be correlated with the degree of nuclear differentiation of the primary tumor. It seemed pertinent to determine whether the relationship between SH and survival in breast cancer was independent of the degree of differentiation of the primary tumor as reflected in the nuclear structure. The nuclei were graded from 0 through 4 in terms of increasing differentiation. The details of the criteria for such grading have been presented elsewhere (5, 10).

In Tables VI through IX we have presented the survival data of breast cancer cases in relation to the nuclear structure, SH grade, and class. Cases of appreciable degrees of lymphoid infiltration in the primary tumor have been excluded. This was done because lymphocytic infiltration has been shown to have a favorable prognostic significance and might, therefore, introduce an additional uncontrolled variable into the analysis. Tables VII and IX are derived from Tables VI and VIII and indicate the percentage of 5 year postoperative survival values as related to the differentiation of the primary tumor (N grade) and the degree of SH. It is evident that increasing nuclear differentiation was associated with increased survival both in the class I and class II cases. This fact confirms previous observations by Bloom and our own laboratory on the prognostic significance of nuclear differentiation. It is also apparent that within each N grade a further prognostic subdivision could be made on the basis of the SH grade. This relationship between SH grade and survival cannot be critically dependent on the amount of lymph node metastases since it is found in the class I as well as in the class II series. In Figures 5 and 6 we have plotted the 5 year postoperative survival values in relation to the N and SH grades. These data clearly indicate that for each of the different

TABLE IX.—PER CENT 5 YEAR POSTOPERATIVE SURVIVAL IN CLASS II BREAST CANCER CASES IN RELATION TO SH AND N GRADE

N grade	*SH grade*							
	Unreadable		*0–1*		*2*		*3–4*	
	No.	*Per cent survival*	*No.*	*Per cent survival*	*No.*	*Per cent survival*	*No.*	*Per cent survival*
0–1	31	15	82	19	12	25	5	80
2	17	47	34	38	15	47	8	88
3–4	10	80	14	57	9	89	4	100

N grades the survival was better in those patients with SH $\geqslant 2$ than in those without such lymph node reactivity.

In Table X we have listed the 5 year survival of patients with other types of cancer who had SH $\geqslant 2$. The survival of the gastric cancer patients with SH was decidedly superior to the usual values cited for resectable gastric carcinoma. It would appear from these data that although SH was uncommon in cancers other than breast, when it was found, the prognostic significance was similar.

There is no question but that the presence or absence of regional node metastases is of prognostic significance in breast cancer and in other cancer types as well. The frequency of regional lymph node metastases has been shown to be correlated with the degree of differentiation of the primary tumor. The possibility exists that the incidence of axillary metastases in breast cancer might also be influenced by the degree of SH reactivity of the regional nodes. In order to evaluate this possibility we determined the frequency of class I cases in relation to SH and the degree of differentiation of the primary tumor. These data are presented in Table X. The over-all incidence of class I cases in this series of 747 cases was 43 per cent, a value

TABLE X.—FIVE YEAR POSTOPERATIVE SURVIVAL OF CANCER PATIENTS (OTHER THAN BREAST) HAVING SH 2

Tumor type	*No. of patients*	*Survivors*	
		No.	*Per cent*
Gastric			
Class I	14	12	86
Class II	10	6	60
Lip	1	0	0
Melanoma	2	2	100
Thyroid	1	1	100
Total	28	21	75

TABLE XI.—PER CENT INCIDENCE OF CLASS I CASES IN RELATION TO SH AND N GRADES OF CANCER

N grade	*SH grade* 0–1		2		3–4		0–4	
	No.	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
0–1	238	28	54	52	28	75	320	36
2	118	32	56	63	26	62	200	45
3–4	71	44	32	63	18	83	121	59
0–4	427	32	142	59	72	72	641	43

consistent with general experience. However, the frequency varied from 28 per cent in patients with anaplastic primary tumors lacking SH to 83 per cent in groups with differentiated tumors associated with SH $\geqslant$ 3. Within each of the nuclear grades, the incidence of class I cases increased with increasing SH. Similarly, when SH was constant the class I cases increased with increasing differentiation of the primary tumor.

It is more reasonable to state that axillary metastases are less common when the primary tumor is well differentiated rather than to state that the presence of such metastases makes the primary tumor anaplastic. In the same sense, the present data would be consistent with the thesis that axillary metastases are less common in patients with SH rather than that axillary metastases removes a pre-existent "normal" sinus reaction. It should be noted that the latter statement does not imply any knowledge of the mechanism of this relationship, viz., immune reactions and physical blockage.

It should also be noted that even in patients with marked tumor differentiation and SH the incidence of class I cases was 83 rather than 100 per cent. Conversely, in those patients having minimal tumor differentiation and no SH the incidence of class I cases was 28 per cent rather than zero. It would appear that factors other than the two considered at this time influence the behavior of breast cancer and favor or deter axillary metastases. Such a viewpoint would be consistent with the more favorable prognosis of the class I over class II cases of similar SH and N grades. In short, the propensity to axillary metastases seems to be an index of, or a crude summation of, the multitude of factors involved in the tumor-host relationship. Among such factors are the differentiation of the primary tumor and sinus histiocytosis of the regional nodes.

To paraphrase Berg: it is agreed that breast cancer patients with axillary metastases have a poorer survival than similar patients without such metastases. The question is whether this association is direct and independent or whether it is dependent upon other more basic associations. Our data indicate that the latter formulation is the correct one and that axillary metastases are a reflection of such factors including the degree of differentiation of the primary tumor, SH of the axillary nodes, and other as yet undefined factors.

In an attempt to provide a further control for our studies of SH we evaluated the degree of follicular prominence in the control lymph nodes and in the long and short survival series of breast cancer cases. The follicular prominence was graded from 0 to 4 in the nodes of each patient and then the case was graded according to the highest grade found in any node. In Table XI, we listed the data obtained from this study.

Follicular hyperplasia was not more frequent in the long survival series than in the control or short survival series. This was in contrast to the findings in the study of SH.

Of 32 breast cancer patients having marked follicular prominence the 5 year survival was only 36 per cent although 15 of these patients did not have axillary metastases. Thus, follicular prominence in the axillary lymph nodes of breast cancer patients was not associated with the same prognostic significance as was SH.

COMMENTS

The present study has indicated that SH is an unusual finding in lymph nodes removed from noncancerous individuals. This viewpoint is substantiated by the lack of reference to such structural features by standard histology texts. It should also be appreciated that even in the cancer cases SH was

noted only in a minority. In the colon and gastric cancer series it was rare while in the breast cancer group it was not found in the majority of cases. Only 11 per cent of the breast cancer cases were graded ⩾3. These data can hardly be said to support the thesis that SH is a normal feature of human lymph nodes.

SH is also infrequent in the lymph nodes of control mice (<5 per cent) whereas it was encountered in about 40 per cent of mice of the same strain bearing spontaneous mammary tumors. Dunn, in her monograph on the normal and pathologic anatomy of the reticular tissue in laboratory mice specifically listed sinus histiocytosis under the heading of "non-neoplastic alterations," subheaded "hyperplasia of particular cell types." Albert and associates in a study of the effects of tumors on lymph nodes in mice commented, "reticulum cell hyperplasia similar to that described by Black, Kerpe and Speer, was found in the nodes from all mice bearing tumors. It was more pronounced in those animals that bore the larger tumors (over 300 sq. mm.). The extent of hyperplasia found in the node did not seem to be related in any way to the location of the tumor, whether in the vicinity of the node examined or at a distant site." Gillman and Gillman in an extensive study of the lymph nodes of rats specifically listed "intense sinus histiocytosis" under the heading, "Some abnormal reactions in lymph nodes." These various data from human and animal studies would favor the designation of SH as a reactive change in lymph nodes. A similar viewpoint was expressed by Spigolon who considered these changes a reflection of "the defense mechanism opposed by the organism to the neoplastic invasion." Gnirs emphasized the reactive nature of sinus histiocytosis in cases of mammary carcinoma and suggested that it might represent a response to a foreign type protein from the carcinoma. He also indicated that the SH reaction was not dependent upon the presence or absence of metastases in the nodes.

Marshall reported that certain cellular

TABLE XII.—PER CENT INCIDENCE OF FOLLICULAR GRADE IN CONTROL AND BREAST CANCER CASES

	Follicular grade, per cent		
Group	*0–1*	*2*	*3–4*
Control	70	19	11
Breast cancer			
Dead 1.5 yrs.	84	10	8
Alive 5 yrs.	74	21	6

elements of lymphoid tissues may be stained by a modification of the Weil-Davenport ammoniacal silver stain. He termed these cells metalophilic cells. Such staining is very prominent in the sinusoids of lymph nodes with some types of syncytial histiocytosis. As designated by Marshall, syncytial histiocytosis is a reactive change of lymph nodes. Judging by his photographs and descriptions it includes sinus histiocytosis as defined.

We have used a modification of Marshall's metalophil technique and have found intense reactions in the sinusoids of lymph nodes with sinus histiocytosis. On the other hand, no such staining was obtained in the sinusoids of lymph nodes with lipogranulomatous changes despite a definite similarity in appearance in hematoxylin and eosin preparations. However, metalophil staining of sinusoidal elements has been observed in some instances of syncytial histiocytosis of types other than sinus histiocytosis. Usually such staining was less intense and of a somewhat different distribution than was found in sinus histiocytosis. A more detailed report of our findings with the metalophil technique will be forthcoming. Suffice it to say at this time that this staining technique provided further evidence that sinus histiocytosis is a manifestation of a distinctive type of lymph node reaction.

In view of these various data it is most suprising that Berg should have stated that, "We have no evidence whatsoever, therefore that histiocytosis as seen in human material is a node reaction at all, much less a response of the host organism that might serve to defend it against cancer." He further concluded, ". . . because histiocytosis was first described in normal nodes, it can

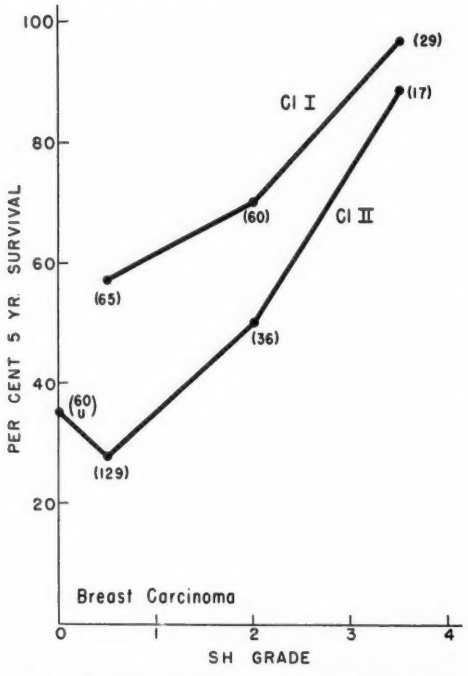

FIG. 4. Per cent 5 year postoperative survival of breast carcinoma patients in relation to SH reactivity of their axillary lymph nodes and the absence (class I) or presence (class II) of axillary metastases.

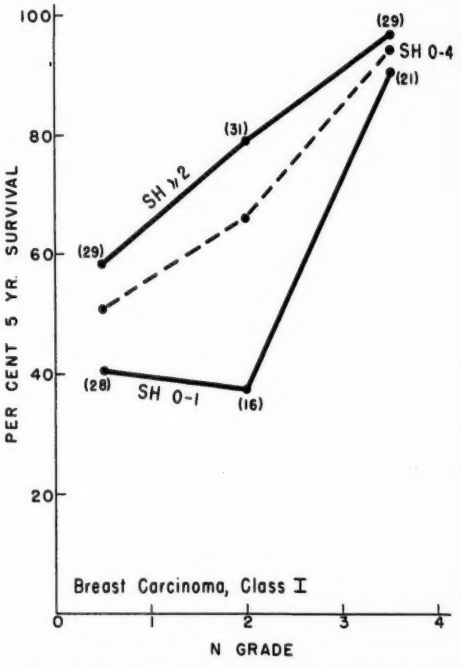

FIG. 5. Per cent 5 year postoperative survival of class I breast cancer patients in relation to the degree of differentiation of the primary tumor (N grade) and the presence or absence of SH of the axillary lymph nodes.

be doubted that this particular pattern of lymph node structure represents a host reaction of any type, meaningful or not." This latter statement refers to the study of Gillman and Gillman and infers that they considered sinus histiocytosis as a normal node pattern. However, as indicated before, these authors distinctly classified it as an example of an abnormal reaction of lymph nodes. It might also be added that the intensity of the SH reaction depicted by Gillman and Gillman (their Fig. 25) would correspond to our SH grade 2.

The contention that the SH-survival relationship is dependent upon the quantity of axillary metastases has been tested by a study of the survival in the class I breast cancer cases. Since these patients have no axillary metastases, it should not have been possible to demonstrate any relationship between SH and survival. However, the data did indicate the existence of distinct differences in the survival of the class I patients having different SH grades, viz., 57, 70, and 97 per cent survival 5 years postoperatively in patients with minimal, moderate, and marked SH respectively. Furthermore, this relationship between SH and survival was not dependent upon the differentiation of the primary tumor as indicated by the data in Figure 5 and Tables VI and VII. Nor should it be claimed to be an expression of the size of the primary tumor since Berg found no statistically significant differences among the 3 year postoperative mortality values in patients with breast cancers of varying size when no axillary nodes were involved or if level I only was positive.

These various data indicate that SH of the axillary lymph nodes of breast cancer patients is of prognostic significance. This association between SH and survival was not dependent upon the amount of axillary metastases, the degree of differentiation or the size of the primary tumor, or the complete surgical eradication of the disease. A similar prognostic significance was also found in regard to SH when it occurred in association with cancer other than breast carcinoma.

While the available data support the reactive nature of SH and its prognostic significance, it should be appreciated that such reactions were rarely seen in the lymph nodes removed with colon carcinomas, even in cases of long survivors. The exact explanation of the varied incidence of regional nodal SH among patients with cancers of different organs is not apparent. However, it is well known that cancers vary in their ability to invoke structural changes in the stromal tissues of the host (desmoplasia). Such local stromal reactions include: minimal stromal alteration as found in some medullary carcinomas, intense fibroblastic activity as in linitis plastica, and intense lymphoid infiltration and follicular metaplasia as exemplified by medullary carcinoma of the breast with lymphoid infiltrate and seminoma. The latter stromal reaction is generally accepted as signifying a favorable prognosis. Such variations in tumor stroma must represent a biologic visualization of subtle differences in the tumor-stromal relationship among individuals, which in special instances (lymphoid infiltration) have prognostic significance. Likewise, the degree of SH seems to reflect individual differences in tumor-host relationships. Whether SH represents an immunologic reaction as suggested by Gnirs cannot be decided on the basis of the present study.

Carcinomas appear to invoke a variety of changes in the regional and perhaps distant lymph nodes. Among such changes are: increase in the number of regional lymph nodes, increased nitrogen retention by the lymph nodes, so-called nitrogen trap effect, increased phosphorus uptake, as well as varied structural changes in the follicles, pulp, and sinuses. It has been noted that SH tends to be more frequent in small and medium sized nodes than in larger nodes. This finding is not inconsistent with the reactive production of additional lymph nodes mentioned. Such newly formed nodes might be particularly expressive of reactive structural patterns.

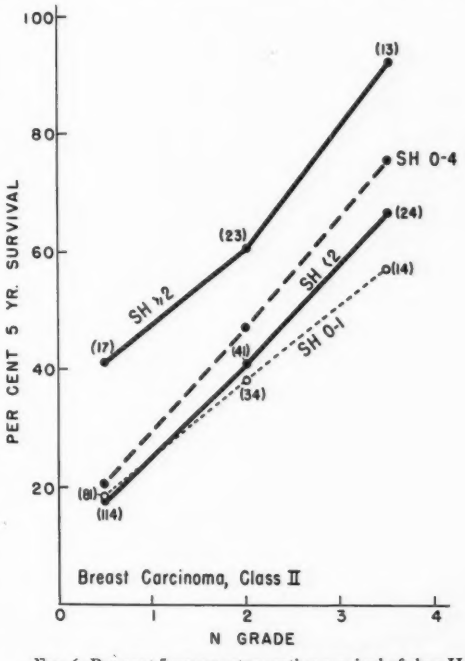

FIG. 6. Per cent 5 year postoperative survival of class II breast cancer patients in relation to the degree of differentiation of the primary tumor (N grade) and the presence or absence of SH of the axillary lymph nodes. Curve SH 2 includes cases with nodes unreadable because of overwhelming metastases as well as those cases read as SH 0–1.

The various data are in accord with our previously expressed opinion that SH of the lymph nodes of cancer patients is a prognostically significant reactive change reflecting a tumor antagonistic status of the host. The genesis and modus operandi of this reaction are not known. However, it does

appear to be a reflection of, or a partial measurement of tumor antagonistic factor(s) of the host. At this time we would re-emphasize the need for continued study of the mechanism of this reaction.

The complexity of factors related to the behavior of cancer has been repeatedly emphasized by this laboratory. With such limitations in mind we would interpret the available data concerning sinus histiocytosis as follows:

1. SH is an uncommon finding in the lymph nodes of cancer-free humans, rats, and mice.

2. SH is more properly considered as representing a reactive change of lymph nodes than as a variant of the normal nodal structure.

3. SH of the regional lymph nodes is greater in breast and gastric cancer patients who subsequently survive for prolonged periods of time than in those who die of the disease within 3 years after surgery.

4. The survival of cancer patients with SH is greater than the survival of similar (N grade and stage) patients without SH.

5. The favorable prognostic significance of SH is not dependent upon the presence or absence or the amount of regional node metastases or the lethality of the primary tumor as expressed in terms of nuclear grade, or the complete surgical eradication of the disease.

6. The survival of breast cancer patients with similar degrees of SH of the axillary nodes varies in relation to the degree of differentiation of the primary tumor and the presence or absence of regional node metastases.

7. Since SH is a reactive change in a tissue of the host and is associated with an increased survival it may properly be termed an expression of host resistance.

SUMMARY

A study was made of the occurrence of sinus histiocytosis (SH) of lymph nodes removed from patients with and without cancer. Within the cancer group the relationship between SH and survival was studied in regard to its dependence upon regional node metastases and the differentiation of the primary tumor. In addition, the pertinent literature was reviewed. The data obtained would seem to justify the following conclusions:

1. SH is an uncommon finding in the lymph nodes of cancer-free humans, rats, and mice.

2. SH is more properly considered as representing a reactive change of lymph nodes than as a variant of the normal nodal structure.

3. SH of the regional lymph nodes is greater in breast and gastric cancer patients who subsequently survive for prolonged periods of time than in those who die of the disease within 3 years after surgery.

4. The survival of cancer patients with SH is greater than the survival of similar (N grade and stage) patients without SH.

5. The favorable prognostic significance of SH is not dependent upon the presence or absence or the amount of regional node metastases or the lethality of the primary tumor as expressed in terms of nuclear grade, or the complete surgical eradication of the disease.

6. The survival of breast cancer patients with similar degrees of SH of the axillary nodes varies in relation to the degree of differentiation of the primary tumor and the presence or absence of regional node metastases.

7. Since SH is a reactive change in a tissue of the host and is associated with an increased survival it may properly be termed an expression of host resistance.

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TWO POSSIBLE CASES OF ACQUIRED HYPOFIBRINOGENEMIA IN THE NEWBORN

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HYPOFIBRINOGENEMIA affecting the mother during the last stages of pregnancy, or during labor, is an uncommon but recognized occurrence. Clinically it may be suspected when there is abruptio placentae associated with maternal collapse, and it may result occasionally in maternal death. The pathology of a fatal case has been reported by Johnstone and McCallum, and of an example in an iso-immunized doe rabbit during labor by Anderson and Johnstone. Histologically the important feature is the occurrence of extensive fibrin deposition within the vessels of the lungs and with occasional involvement of other organs such as the kidneys.

This condition is thought to be produced by the sudden massive escape into the maternal circulation of thromboplastin of decidual origin which initiates intravascular clotting. It is reasonable to suggest that the same process occurring less dramatically may be responsible for fibrin deposition seen so commonly in placentae. If this is the correct explanation, there is no reason why the fetal circulation should not absorb some of the released thromboplastin, and thus a certain number of neonatal deaths may be due to acquired hypofibrinogenemia affecting the fetus.

To examine this possibility, postmortem material from full term neonatal deaths and from prematurely born infants dying within a few days of birth in Stirlingshire, Scotland, in the last 4½ years was re-examined histologically. Material for histologic examination had not been taken in every case, but is available for 47 cases, these being divided as follows: 30 neonatal deaths (less than 48 hours after birth), and 17 premature infants (longest survival being 6 days).

Only neonatal deaths occurring within 48 hours of birth among the full term infants have been considered in this survey, because it has been shown by Drury and McMaster that fibrinogen depletion can be replenished within 5 to 6 hours. On the other hand, all available neonatal deaths among premature infants were incorporated in the series on the hypothesis that premature infants may not show the same capacity for replenishing fibrinogen loss.

Sections were stained with hematoxylin and eosin, and Lieb's phosphotungstic acid hematoxylin for fibrin. When the presence of fibrin was suspected, it was confirmed by Weigert's stain for fibrin and by Masson's trichrome method.

Pulmonary intravascular fibrin deposits were found by this procedure in 10 cases. In 2 of these, the lesions were numerous, clearly ante mortem, and resembled those seen in maternal hypofibrinogenemia. In 4 cases there were similar but scantier lesions. In the remaining 4 cases fibrin deposits were seen, but it is not possible to state confidently at this stage that they occurred before death or at least in the agonal period.

CASE REPORTS

CASE 1. The mother was a secundigravida with blood group O, Rh negative, antibody titer 1/128 in albumin latterly. Delivery was normal but mild postpartum hemorrhage occurred.

The male infant lived less than 1 day. He was gray and limp at birth. The cord blood hemoglobin was 36 per cent (5.3 grams per cent). Many erythroblasts and other nucleated red corpuscles were present. Improvement occurred during replacement transfusion, but the infant collapsed suddenly near the end of it and coughed up blood-stained mucus. At postmortem examination of this full term infant the lungs were

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FIG. 1. Dense intra-arteriole fibrin clot in lung (Case 1). Phosphotungstic acid hematoxylin, × 186.

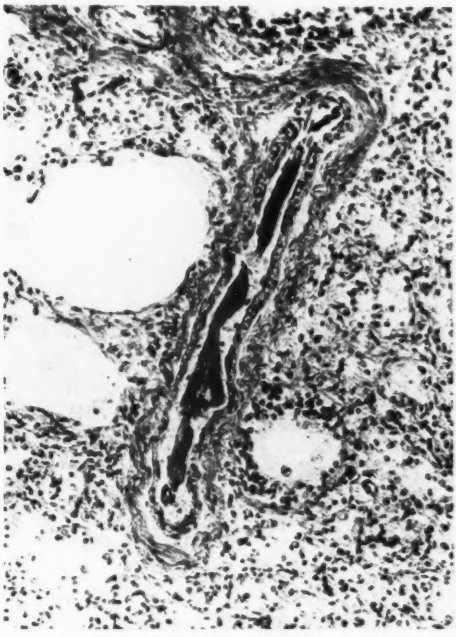

FIG. 2. Intravascular fibrin clot in pulmonary arteriole (Case 2). Phosphotungstic acid hematoxylin, × 186.

not fully expanded, and the right side of the heart was dilated. There was some splenic enlargement, but no abnormality in the head. The diagnosis was: erythroblastosis fetalis, cardiac failure, atelectasis. Histologic examination revealed the presence of widespread antemortem intravascular fibrin emboli in the lungs (Fig. 1) and also in the hepatic sinusoids. Doubtful emboli were present in the brain, thyroid, and thymus glands. No emboli were found in the myocardium, spleen, or kidney.

CASE 2. The hypertensive and edematous mother was admitted with a twin pregnancy at 26 weeks because she was draining blood stained liquor. Labor started 16 days later and male twins were delivered. The placenta was uniovular and there was no retroplacental hematoma.

Premature twin No. 1 lived less than 1 day. At postmortem examination the lungs showed patchy aeration and atelectasis. A blood-stained serous right pleural effusion was present. The abdomen and head showed no abnormality. The diagnosis was prematurity and atelectasis. Histologic examination revealed the presence of extensive intravascular pulmonary fibrin emboli (Fig. 2). No other organs were examined.

Twin No. 2 died fully 24 hours after birth. Postmortem examination showed only prematurity and atelectasis. No fibrin emboli were found in the lungs.

DISCUSSION

Potter drew attention to pulmonary ecchymosis in the newborn in association with antepartum hemorrhage and retroplacental hematoma, and Bound, Butler, and Spector gave a very lucid description of neonatal deaths due to the "pulmonary syndrome." In this condition the baby is in poor condition at birth in many cases, and all show cyanosis accompanied by respiratory distress. The babies in their series who showed these features most frequently were premature and were born by cesarean section.

It is interesting that the present 2 cases, studied, first, from the histologic viewpoint and, second, by examining the case notes, were found to have histories very similar to those of the so-called pulmonary syndrome.

One of the mothers had a mild postpartum

hemorrhage, while the other, with a twin pregnancy, was admitted draining blood stained liquor. It is interesting to note that in this last example fibrin deposits were found in one twin but not in the other. If this finding is due to the hypofibrinogenemia mechanism, one may assume that a certain degree of premature separation of the area of the placenta supplying twin No. 1 occurred, with associated absorption of released decidual thromboplastin.

In the large series by Bound and associates the incidence of the "pulmonary syndrome" was 27 per cent. My series of 47 cases does not include all babies dying and coming to postmortem examination within 1 month of birth, but nevertheless it has revealed 6 cases (13 per cent) showing histologic features similar to those seen in maternal hypofibrinogenemia. In the 2 cases reported herein, the intravascular fibrin emboli are extensive, and in the other 4 cases the lesions are less extensive, but probably contributed to the difficulties of survival.

If the appearances described are in fact due to the same mechanism as in maternal hypofibrinogenemia, the following assumptions are permissible: (a) the rarity of intravascular thrombosis affecting the fetal vessels of the chorionic villi can be explained by the delay, estimated at 10 to 60 seconds, between the entry of the thromboplastin and the formation of intravascular clots in the fetal blood stream which is moving and thus carrying the thromboplastin away from the placental site; (b) for the same reason, the fibrin may not be precipitated entirely in the pulmonary arteries, but may be found also in the pulmonary veins. This variation in the histologic features may be noted, not only from patient to patient, but in different areas and tissues in the one patient; (c) considering the small blood volume of the newborn baby (300 ml.) in comparison with that of its mother (6,000 ml.), only a small quantity of thromboplastin is required to produce a fatal outcome in the baby, whereas this small quantity entering the maternal circulation may not cause any clinical upset; (d) since the lungs are the most severely damaged organs, and the organs affected most commonly, it would appear that thromboplastin does not enter the fetal circulation until the fetal circulation converts to the adult form, i.e., once the head has been born and air has been inspired; and (e) when the condition is extensive in the lungs, microinfarcts are produced, which are hemorrhagic and may become confluent. Pneumonia may therefore complicate the picture, and it is my impression from study of the 37 "negative" cases that intravascular fibrin emboli may be digested by fibrinolysins of bacterial origin.

Proof of the hypothesis that acquired hypofibrinogenemia may occur in the newborn infant must await confirmation by biochemical methods.

SUMMARY

As an incidental finding in 2 neonatal postmortem examinations, intravascular thromboses similar to those found in maternal hypofibrinogenemia were seen.

A mechanism which could result in acquired neonatal hypofibrinogenemia is discussed.

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SURGICAL EXPERIENCES IN THE TREATMENT OF ANEURYSMS OF THE THORACIC AORTA

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THE RATIONALE OF EXCISIONAL THERAPY for aortic aneurysms has been clearly established. Surgical experience with this disease, however, has been concerned primarily with aneurysms of the abdominal aorta. Aneurysms of the thoracic aorta have been attacked with more reluctance by surgeons, although more than 50 years ago Tuffier ligated the neck of a saccular aneurysm of the ascending aorta.

The poor prognosis of untreated thoracic aneurysms justifies surgical intervention. Unfortunately, accurate statistics are available only for syphilitic aneurysms. According to Kampmeier, the average period from onset of symptoms to death in patients with syphilitic aneurysms is 6 to 9 months. A somewhat less gloomy, but still foreboding, picture is offered by Cranley and associates for patients suffering from this disease. Of 169 patients with syphilitic aneurysms of the thoracic aorta studied at necropsy, death was due to the aneurysm in 79. One is justified, it appears, in assuming that arteriosclerotic aneurysms, as well as congenital and traumatic aneurysms, have an equally poor prognosis.

Bahnson (2) and Cooley and DeBakey (5) have reported encouraging results in the treatment of thoracic aneurysms by lateral excision and aortorrhaphy, as well as by resection and homograft replacement. With few exceptions, however, the majority of the published reports on resection of thoracic aneurysms has dealt with isolated cases only. It is difficult from such isolated reports to appraise the proper role of excisional therapy in the management of these lesions. We have attempted, therefore, to view the problem in the perspective of experiences gained in the management of 20 cases of thoracic aortic aneurysm. These patients underwent surgical exploration in the 3 year period from January 1, 1954 through December 31, 1956. Eighteen of the patients were males and 2 were females. Their ages ranged from 5 to 71 years. Almost two-thirds of the patients were in the sixth, seventh, and eighth decades of life.

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TYPES OF ANEURYSMS

A wide variety of aneurysms are represented in this relatively small group of patients distributed as follows: arteriosclerotic aortic aneurysms 7, syphilitic 5, traumatic 3, congenital 2, mycotic 2, and dissecting 1. Unlike most reported series, in which syphilitic aneurysms predominate, arteriosclerotic aneurysms were the most common. It seems likely that fewer syphilitic aneurysms of the thoracic aorta will be encountered as antisyphilitic therapy becomes more widespread and that arteriosclerotic aneurysms will increase as the over-all age of the general population increases.

Arteriosclerotic aneurysms are usually fusiform and more often involve the distal part of the aortic arch and the descending aorta than the proximal portions of the aorta. Six of the 7 arteriosclerotic aortic aneurysms involved the aorta distal to the left subclavian artery while 1 involved the distal part of the aortic arch in the region of origin of the left common carotid artery and left subclavian artery. The average age of these patients was 61.7 years.

There were 5 syphilitic aneurysms in this group of patients. Classically, aneurysms of this type occur in the ascending aorta and the aortic arch. Although they are often saccular in form and have a narrow mouth, such was not true in these 5 cases. None, therefore, was suitable for lateral excision and aortorrhaphy. Two of these aneurysms involved the proximal portion of the aortic arch, while the others arose distal to the left subclavian artery. The average age of these patients was 59.6 years.

Traumatic aneurysms were noted in 3 patients. Aneurysms of this type are most commonly located at the top of the descending aorta just distal to the origin of the left subclavian artery and at the site of the ligamentum arteriosum. Two of the 3 aneurysms in this group were so located. Another common site is the ascending aorta just distal to the aortic valve. Both of these sites are relatively fixed points and are placed under stress during deceleration. The third aneurysm in this group occurred at the origin of the innominate artery. Two of these patients were young, aged 30 and 37 years, while the third was 66 years old. Aneurysms of this type are more likely to occur in younger people than are the 2 previously discussed varieties.

Two patients had congenital aneurysms. These are rare and may be of the aortic sinus type or they may arise in the region of the ligamentum arteriosum. Both of these aneurysms were of the latter variety and they occurred in patients 21 and 34 years of age.

There were 2 patients with mycotic aneurysms, 1 occurring distal to a site of coarctation and 1 occurring at the suture line following resection of a coarctation of the aorta and end-to-end anastomosis performed elsewhere. The final patient had a dissecting aneurysm of the proximal portion of the descending aorta.

DIAGNOSIS

Symptoms were present in 14 of these 20 patients but were not diagnostic. The usual symptoms were the expected ones, namely, pain and thoracic discomfort, cough, dyspnea, hoarseness, and dysphagia. Hemoptysis was rare. The patients with mycotic aneurysms complained chiefly of chills and fever. The diagnosis rests on the interpretation of routine roentgenograms of the thorax and the proper use of ancillary roentgenographic methods.

The differentiation of mediastinal tumor and thoracic aneurysm may be difficult. The presence or absence of pulsation of the mass was found to be an unreliable aid in diagnosis.

In this study of thoracic aneurysms of the distal part of the aortic arch and the descending aorta, upright thoracic roentgenograms taken at multiple angles, either in the right posterior oblique or left anterior oblique projection, were particularly valuable in clarifying the nature and location of the lesion. These views are profitably supplemented by 1 or 2 right anterior oblique views, a lateral view, and a posteroanterior projection taken by the Bucky technique.

When the ascending aorta and proximal portion of the aortic arch are studied, roentgenoscopy and roentgenography are less helpful. It is here that the procedure of retrograde aortic catheterization and aortography is particularly useful. In patients who are not very large, the simpler method of venous angiocardiography may yield excellent results. By outlining the aorta with opaque material, information relative to the status of the wall of the aorta (for example, thickness of clot) and extent of involvement may be obtained.

OPERATIVE EXPERIENCE

Resectability. Fifteen of the 20 aneurysms under review were treated by resection, a resectability rate of 75 per cent. The location of the aneurysm was of prime importance in this regard (Fig. 1). Four aneurysms that involved the proximal or transverse portion of the aortic arch were not subjected to resection because of the danger of interfering with cerebral blood flow. It was

hoped prior to exploration in these patients that lateral excision and aortorrhaphy could be undertaken. The fifth aneurysm was incorrectly judged at the time of exploration to arise too close to the left common carotid artery to permit safe excision. Successful excision of this aneurysm was carried out later at another institution.

Technique employed. A variety of incisions were used in these cases, depending on the location of the aneurysm. Aneurysms of the ascending aorta and aortic arch were exposed by a bilateral anterior thoracotomy, the sternum being divided. The thorax was entered through either the third or the fourth intercostal space. In lesions of the distal part of the arch or upper part of the descending aorta, an incision through the left fourth intercostal space was used. The left fifth or sixth intercostal space was entered to expose aneurysms of the mid portion of the descending aorta, while aneurysms of the distal portion of the descending aorta were approached through the seventh intercostal space. If necessary, the latter incision was lengthened into a thoracoabdominal one when the aneurysm extended below the diaphragm. For large aneurysms involving the entire descending aorta the sixth rib may be resected and the angles of one or two ribs above and below divided for wide exposure. Good exposure is essential in the management of these cases and it is frequently necessary to divide at least one rib posterior to the angle when an intercostal incision is used.

One of the problems associated with operations requiring cross clamping of the thoracic aorta is that of spinal cord ischemia. Various methods have been employed to avoid this complication. Pontius and his associates have indicated the value of hypothermia in this regard. Hypothermia was the most common method employed in the series under review, 12 patients being operated on in such a manner.

Body temperature was lowered in these 12 patients by covering them with a rubber blanket through which cold water was circulated. An attempt was made to lower the temperature to between 32 and 34 degrees C. before the beginning of rewarming by the circulation of warm water through the blanket. The temperature usually dropped an additional 2 degrees, resulting in a final temperature of 30 to 32 degrees C. Actually, temperatures of the patients operated on varied from 26.5 to 30.1 degrees, with an average of 29 degrees C. being somewhat lower than desired.

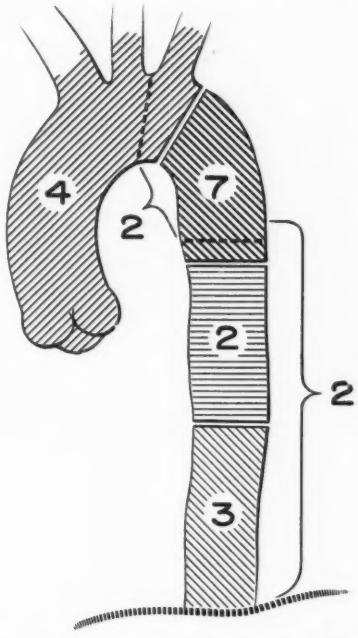

FIG. 1. Location of 20 aneurysms under review.

Of the remaining 8 patients, 2 had adequate collaterals because of coarctation of the aorta and were not cooled. Two patients were operated on under normothermic conditions, with a mistaken diagnosis of an anterior mediastinal tumor. The aneurysms were not excised because of involvement of the cerebral vessels. Two other patients who were operated on under normothermic conditions in the hope of carrying out lateral excision and aortorrhaphy were found to have aneurysms that were inoperable for

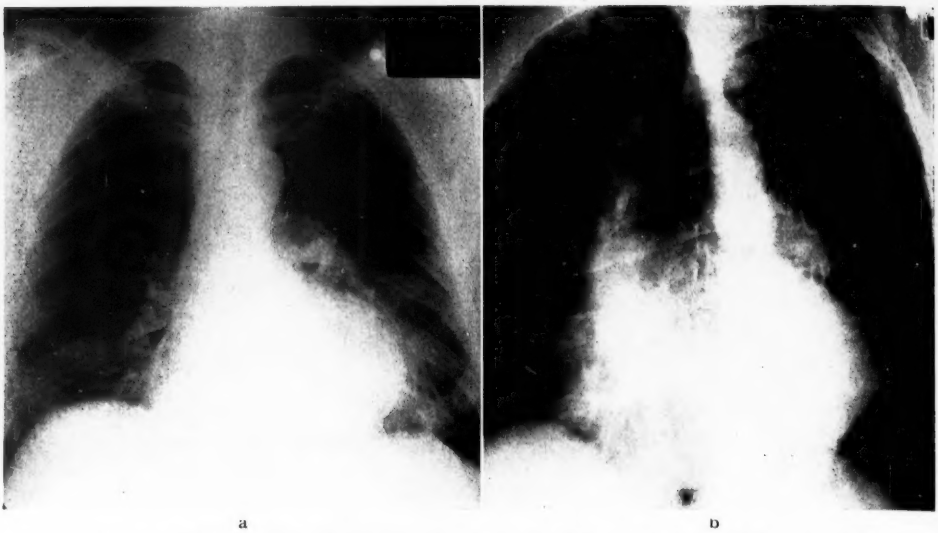

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FIG. 2. Case 1. Thoracic roentgenograms of 66 year old man with arteriosclerotic aneurysm of aorta. a, Posteroanterior projection. b, Left anterior oblique projection.

similar reasons. A saccular aneurysm of the distant part of the aortic arch was removed from another patient under normothermic conditions by lateral excision and aortorrhaphy. The final patient was operated on under normothermic conditions, circulation being maintained during the period of aortic occlusion by means of a bovine shunt.

Of the 15 patients who underwent resection, grafts were employed in all but 1 patient who underwent lateral excision and aortorrhaphy. Homologous aortic grafts preserved by a method previously described (4) were employed in 12 patients and polyvinyl formal (ivalon) grafts were used in 2 patients. End-to-end anastomoses were performed with running No. 3-0 or 5-0 vascular silk sutures interrupted at the angles. Aortic occlusion time varied from 40 to 90 minutes, averaging 56 minutes.

Mortality and morbidity. There were 5 hospital deaths in this group of 15 patients undergoing resection and grafting, a mortality rate of 33.3 per cent. Hemorrhage, hypothermia, or a combination of the two resulted in 4 of the 5 deaths.

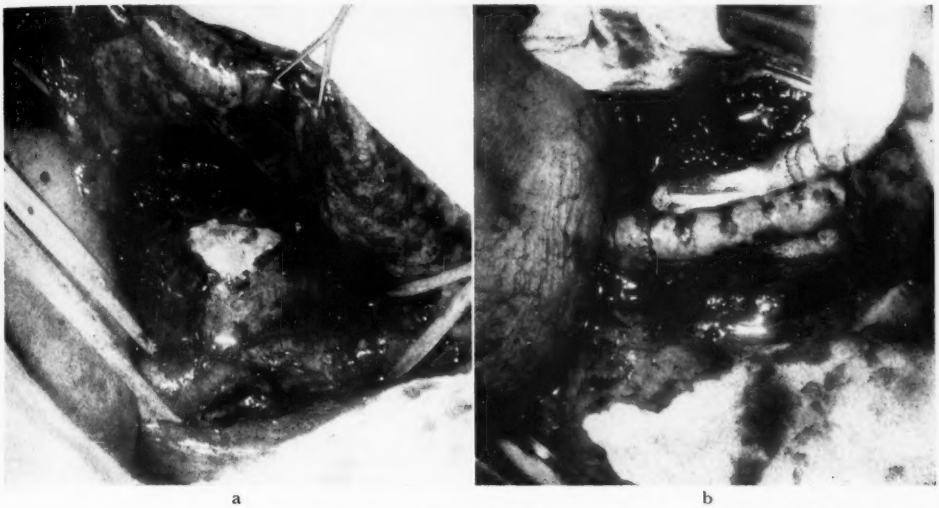
One death occurred in a 62 year old man with an arteriosclerotic aneurysm of the descending aorta. Massive hemoptysis developed and he died suddenly 1 month after operation. Postmortem examination revealed separation of the lower anastomosis.

The second death occurred in a 66 year old man with a syphilitic aneurysm of the descending aorta. In situ thrombosis occurred in the descending aorta during insertion of a polyvinyl formal graft. Although the vessel was freed of clot and circulation was re-established, the patient's temperature drifted slowly downward, and he died soon after the thorax was closed.

A 66 year old woman with an arteriosclerotic aneurysm of the descending aorta died of ventricular fibrillation. Hemorrhage occurred during excision of the aneurysm. It was controlled but the patient's body temperature began to drop. Ventricular fibrillation developed which could not be broken.

The fourth death occurred in a 50 year old man with a dissecting aneurysm of the distal part of the aortic arch. It took place on the operating table from hemorrhage of the ascending aorta at the suture site of a bovine shunt employed to bypass temporarily the aneurysm during resection.

The final death occurred 8 hours after operation in a 65 year old man with a syphilitic aneurysm requiring excision of the entire descending aorta from the subclavian artery to the diaphragm. He recovered satisfactorily from the anesthesia and moved all extremities normally. Persistent ooze of blood from the thorax occurred and, in spite of transfusions, hypo-



a b

FIG. 3. Case 1. a, Appearance of arteriosclerotic aneurysm at operation. b, View of operative field after insertion of aortic homograft.

tension progressed and death ensued. The graft was intact at the time of postmortem examination and no single source of bleeding could be found.

There was one significant complication:

A 37 year old man underwent resection and grafting under hypothermia for a traumatic aneurysm of the distal aortic arch. Aortic occlusion time was prolonged, totally 90 minutes. Definite weakness of both lower extremities was noted immediately postoperatively. This gradually improved with physical therapy, and the patient is now able to work full time and walk with the use of a cane.

With 1 exception, all the patients who survived resection and grafting have remained in good health to the time of the present report. The follow-up period has varied from 1 year to 30 months, averaging 19 months. The one exception mentioned deserves special comment:

A 56 year old man with a saccular traumatic aneurysm of the aorta just distal to the left subclavian artery successfully underwent lateral excision and aortorrhaphy. He returned for re-examination 2 years after operation, at which time recurrence of the aneurysm was suspected from the thoracic roentgenogram. Two months later he died suddenly at home of a massive hemorrhage, presumably from rupture of the recurrent aneurysm.

REPORT OF ILLUSTRATIVE CASES

CASE 1. *Arteriosclerotic aneurysm.*—A 66 year old railroad foreman entered the hospital with a chief complaint of claudication in the left leg. His family history and his past history were noncontributory. The onset of claudication in the left calf was noted several years previously. It was progressive in nature, and at the time of examination he could walk less than a block without pain.

The results of physical examination were negative except for absence of pulses in the left lower extremity below a normally palpable femoral pulse. Laboratory examination of the urine, hemoglobin, erythrocytes, and leucocytes gave negative results. X-ray examination revealed a poorly functioning gallbladder with

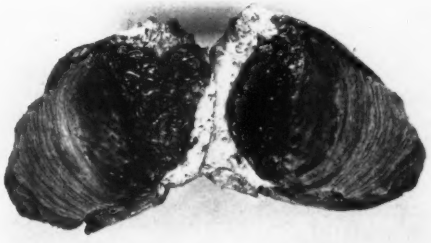


FIG. 4. Case 1. Specimen opened after resection, illustrating presence of laminated clot.

FIG. 5. Case 2. Thoracic roentgenograms of 65 year old man with huge syphilitic aneurysm involving the entire descending thoracic aorta. a, Posteroanterior projection. b, Lateral projection. c, Bucky posteroanterior view. d, Lateral view demonstrating esophageal obstruction.

stones. Thoracic roentgenograms disclosed a large aneurysm of the descending thoracic aorta just above the diaphragm (Fig. 2).

Operation was undertaken with the patient's body temperature lowered to 28 degrees C. The left side of the thorax was entered through the seventh intercostal

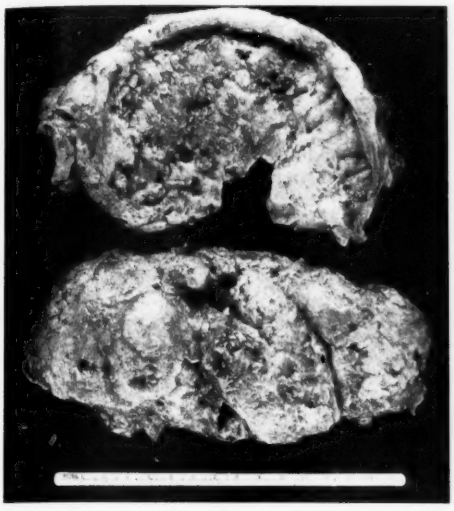


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FIG. 6.

FIG. 6. Case 2. a, Aneurysmal wall and clot removed. b, View of graft in place at time of operation. Aneurysm still in place.

FIG. 7. Case 2. Graft and upper anastomosis after removal of aneurysm. Note eroded vertebrae at bottom of picture.

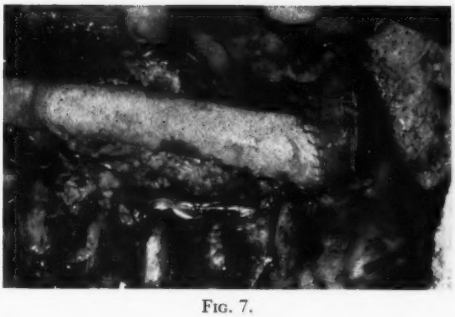


FIG. 7.

space. The angles of the sixth and seventh ribs were divided for better exposure. A large aneurysm was encountered extending from about the sixth thoracic vertebra to a short distance from the diaphragm (Figs. 3a and 4). It invaded the lung anteriorly. The aneurysm was freed from the surrounding structures, clamps were placed above and below, and it was excised. A preserved homologous aortic graft was inserted, both anastomoses being carried out with running No. 000 silk sutures interrupted at the angles and reinforced with interrupted stitches of No. 6-0 silk (Fig. 3b). The clamps were removed, having been in place for 55 minutes. There was minimal bleeding from the suture line, and the thorax was closed in layers after insertion of an intercostal tube for postoperative drainage. A total of 3,500 cubic centimeters of cross-matched blood was used during the course of operation.

The patient's postoperative course was entirely uneventful. The rewarming period was completed without event. The thoracic tube was removed on the fifth day, and the patient was dismissed from the hospital on the eleventh day after operation.

He has remained well for the past 2 years although he has continued to have claudication in the left leg. He has been advised to have treatment for this, as well as for gallstones.

This case illustrates a type of arteriosclerotic aneurysm of the aorta eminently suitable for resection and grafting. Lesions in this location may be dealt with relatively easily, and the results should be good.

CASE 2. *Syphilitic aneurysm.*—A 65 year old blacksmith was admitted for treatment of a thoracic aortic

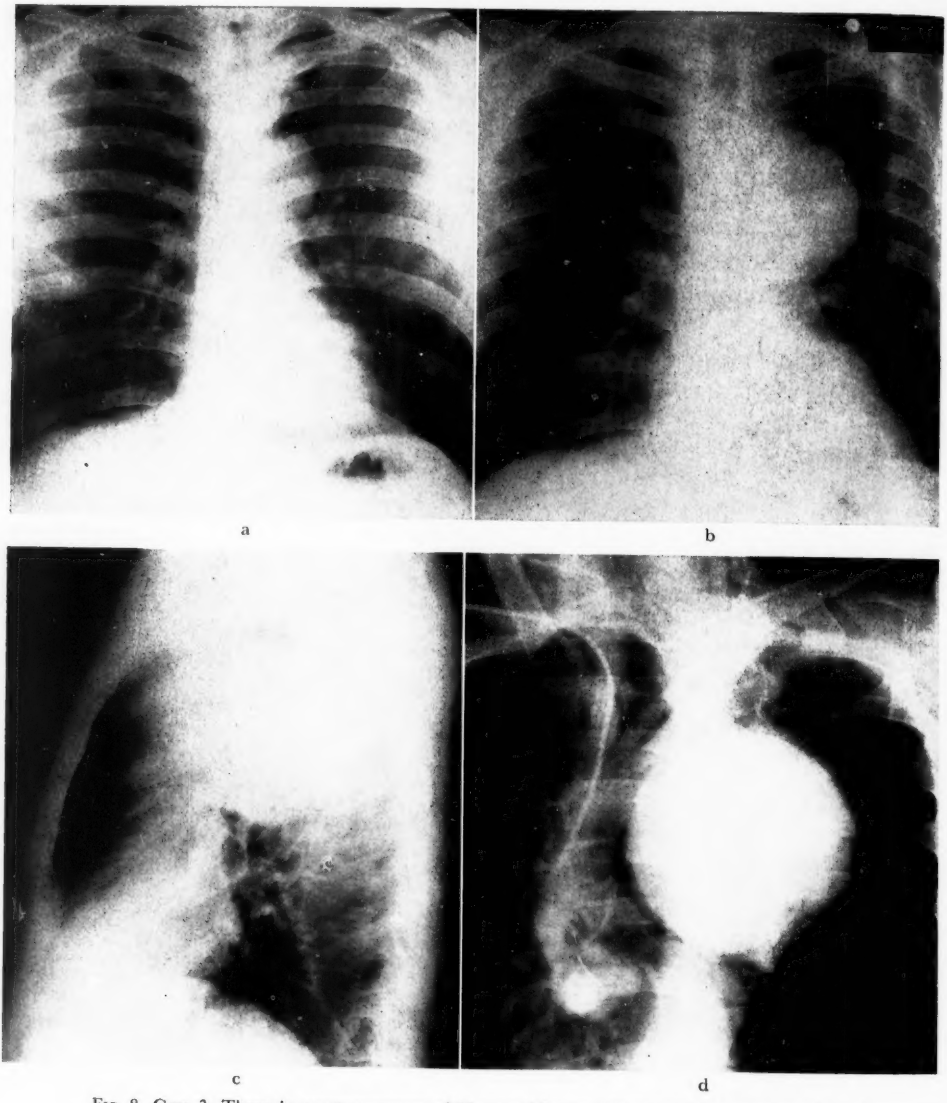


FIG. 8. Case 3. Thoracic roentgenograms of 37 year old man with traumatic aneurysm of distal part of aortic arch. a, Posteroanterior projection 6 years before operation. b, Similar projection immediately prior to operation. c, Lateral view. d, Retrograde aortogram showing filling of aneurysm and origin distal to left subclavian artery.

aneurysm. He had been well until the development of a "pressure" sensation in the left lower part of the thorax 5 months before admission. This discomfort had increased in severity since its onset. Progressive dysphagia to solid foods, of 5 months' duration, was also noted. This was associated with frequent regurgitation of undigested food. A weight loss of 40 pounds had resulted. The past history was negative except for a diagnosis of syphilis made 32 years before. Treatment had been inadequate.

Physical examination revealed a slightly anemic-appearing elderly man showing evidence of loss of weight. There was a tracheal tug. The entire left side of the thorax exhibited prominent pulsations to palpation. A grade 1 systolic murmur was audible over the entire precordium.

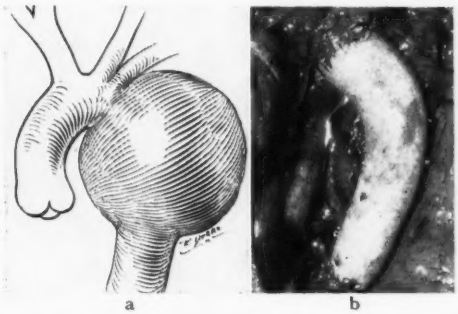
Laboratory examination disclosed a hemoglobin concentration of 10.9 grams per 100 cubic centimeters. The erythrocyte count was 4,460,000 and the leucocyte count 10,700 per cubic millimeter. The sedimentation rate was 77 in the first hour (Westergren method) and urinalysis gave negative results. The Kahn reaction was 4 plus.

A thoracic roentgenogram revealed a large mass in the posterior mediastinum (Fig. 5), and pressure erosion of the anterior aspects of bodies of sixth, seventh, and eighth thoracic vertebrae. Expansile pulsations were visible on fluoroscopy. The esophagus was deviated anteriorly, and delay in the passage of ingested barium was noted. A gastric and a duodenal ulcer were also present.

Preoperative preparation consisted of penicillin therapy for syphilis as well as transfusion of 3 units of blood.

Operation was undertaken under hypothermia. The intraesophageal temperature reached 28 degrees C. The left side of the thorax was entered by means of a long posterolateral incision through the bed of the resected sixth rib. The angles of the fourth, fifth, and seventh ribs were divided for better exposure. A huge aneurysm was encountered, extending from just below the origin of the left subclavian artery to just above the diaphragm (Fig. 6). The proximal and distal portions of the aorta were dilated. After partial dissection of the aneurysm from the thoracic wall and the lung, clamps were placed above and below the aneurysm and it was partially removed. A previously prepared thoracic aortic homograft was sutured in place with No. 000 running silk sutures interrupted at each angle (Fig. 6b). A wedge of distal aortic wall was excised to narrow its lumen prior to anastomosis. The clamps were removed and blood flow re-established after 48 minutes. The remainder of the aneurysmal sac was then removed, baring the eroded bodies of several vertebrae (Fig. 7). Rewarming was begun by flooding the thoracic cavity with warm saline solution. The thorax was closed in layers, an intercostal tube being left in each pleural space. The patient's temperature was then restored to normal by warm water circulating through the coils of a rubber blanket. A total of 6,000 cubic centimeters of blood was administered.

The patient awoke from the anesthesia, responded well, and moved his extremities without difficulty. Although the thorax had been relatively dry at the conclusion of the procedure, bloody drainage persisted from the thoracic catheter in the postoperative period. The blood pressure fell in spite of supportive efforts, and the patient died 8 hours after operation.



a b

FIG. 9. Case 3. a, Diagram of extent and location of aneurysm. b, Appearance at operation after graft insert.

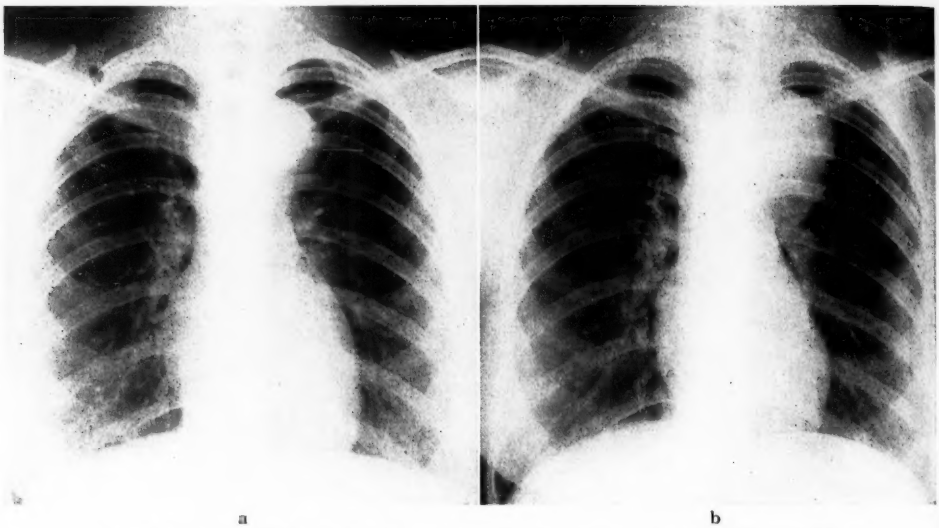
Postmortem examination revealed a total of 1,500 cubic centimeters of blood in both pleural spaces. The graft was intact and no leakage could be demonstrated at the anastomotic sites.

This extensive operation was carried out on a poor risk patient. Had blood replacement been adequate, he might have survived. Excision of the entire descending thoracic aorta is fraught with many risks, spinal ischemia being one of the major dangers. This patient showed no evidences of paralysis following recovery from the anesthesia.

CASE 3. *Traumatic aneurysm.*—A 37 year old merchant was first seen because of thoracic pain that had begun 4 days previously. His past history revealed that in 1943, while he was a pilot in the war, his plane had crashed at sea. He was hospitalized for several weeks following this, but at the time of discharge from the armed services a thoracic roentgenogram was reported as disclosing no abnormality. Another thoracic roentgenogram which was made 6 years before admission showed enlargement of the aortic knob shadow (Fig. 8a).

He described the thoracic pain as being sudden in onset, stabbing in nature, and located in the precordial region. The pain subsided but recurred 2 days later, at which time his physician had a thoracic roentgenogram made.

The results of physical examination at the time of admission were within normal limits. Laboratory examination of the hemoglobin, leucocytes, and urine revealed normal values. A thoracic roentgenogram demonstrated a large, smooth, spherical mass in the region of the aortic arch on the left (Fig. 8b and c). At fluoroscopic examination, pulsations were visible. A retrograde aortogram made via the right brachial artery demonstrated filling of the mass by injected dye



a b

FIG. 10. Case 4. Thoracic roentgenograms of 28 year old woman with congenital aneurysm of aorta. a, Posteroanterior projection made 7 years before operation. b, Same projection immediately prior to operation, demonstrating enlargement of aneurysm.

(Fig. 8d). The lesion was seen to arise just beyond the left subclavian artery.

Operation was carried out with the patient's body temperature lowered to 30.5 degrees C. A long posterolateral incision was made on the left, and the thoracic cavity was entered through the fourth intercostal space. A huge aneurysm, 10 centimeters in diameter, was located in the distal portion of the aortic arch (Fig. 9a). It was adherent to the lung. The aneurysm was dissected free. A clamp was placed between the left common carotid artery and the subclavian artery, another on the subclavian artery, and a third below the aneurysm. The lesion was removed. An homologous aortic graft was inserted, both anastomoses being carried out with running No. 5-0 silk sutures interrupted at the angles (Fig. 9b). The left subclavian artery was preserved. The clamps were removed, having been in place for 90 minutes. A total of 2,500 cubic centimeters of blood was used during the procedure. The thorax was closed in layers after an intercostal tube had been placed for drainage.

The rewarming period was uneventful and the patient was returned to his room in good condition. It was apparent the following day that although the patient could move his legs, there was considerable weakness present. His postoperative course was otherwise uneventful. Considerable improvement occurred with physical therapy, and after several months he was able to return to full time work which he now continues, 1 year after operation.

The safe period of aortic occlusion under hypothermia was exceeded in this case. Although many variations in response to aortic occlusion occur, it is best not to exceed 1 hour.

CASE 4. *Congenital aneurysm.*—A 21 year old woman came to the Mayo Clinic because of the finding of a thoracic lesion on a survey thoracic roentgenogram 15 months previously. About 10 months prior to seeking medical advice, she began to notice occasional episodes of left anterior thoracic pain.

Physical examination disclosed a systolic murmur at the second left intercostal space. Also, a thrill was audible in the suprasternal area on forward bending. Laboratory examination of the urine, hemoglobin, and leucocytes gave negative results. A thoracic roentgenogram revealed a mass at the level of the aortic arch (Fig. 10a). Angiocardiography proved this to be an aneurysm.

The patient was allowed to return home, and she remained well until she delivered a child 5 years later after which she again noted left anterior thoracic pain. This became more severe 2 years later. Because the pain continued for 5 to 6 months, she returned for reexamination.

Physical findings remained unchanged. A thoracic roentgenogram revealed considerable enlargement of the aneurysm (Fig. 10b) and operation was advised.

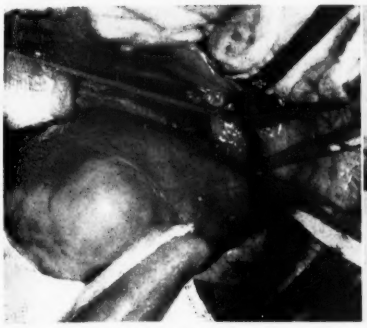


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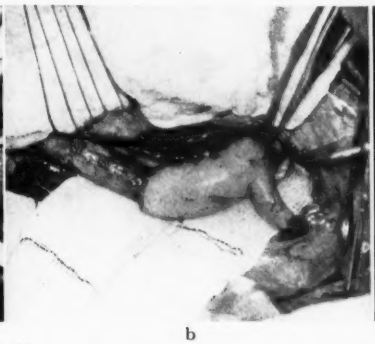
FIG. 11.



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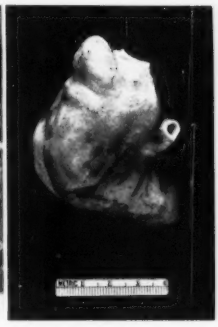

FIG. 12.

FIG. 11. Case 4. a, Appearance of congenital aneurysm at operation. b, Graft in place at time of operation. The left subclavian artery was sutured to a branch of the graft.
FIG. 12. Case 4. Excised aneurysm.

The patient's body temperature was lowered to 28.5 degrees C. The left side of the thorax was entered through the fourth intercostal space. There was a large aneurysm beginning just distal to the ligamentum arteriosum (Figs. 11a and 12). The left subclavian artery arose from the aneurysm. The lesion was dissected free. The ligamentum arteriosum was ligated and divided. Clamps were placed on the aorta above and below the aneurysm and on the left subclavian artery. The aneurysm was excised. A preserved homograft of the arch of the aorta including the left subclavian artery was sutured in place, all three anastomoses being made with running No. 5-0 silk sutures (Fig. 11b). The thorax was closed in layers after insertion of an intercostal tube for drainage. A total of 1,500 cubic centimeters of blood was used.

The patient's subsequent course was uneventful, and she was dismissed 2 weeks after operation. Fourteen months later she remained well.

Enlargement of the aneurysm was clearly demonstrated in this case over a period of 7 years of observation. Rupture would undoubtedly have occurred, had surgical treatment not been carried out.

COMMENT

Our experience with the surgical management of thoracic aortic aneurysms is limited, and no final conclusions should be drawn from this material. However, certain views can be expressed as tentative guides for future use.

As already pointed out, roentgenology plays a useful role in the diagnosis of this disease. A variety of symptoms may be present, few of which are specific. Once the diagnosis has been made, the roentgenologist next must attempt to indicate to the surgeon whether or not the great vessels are involved. This knowledge will influence the surgical approach or may even indicate inoperability. In aneurysms of the descending thoracic aorta, roentgenograms taken in projections previously described often suffice. Aneurysms of the ascending aorta are preferably evaluated by angiocardiography or retrograde aortography. Aneurysms that arise in the distal portion of the aortic arch give the roentgenologist the most difficulty. Even after opacification he may find it difficult to define the exact relationship of the aneurysms to the great vessels.

At the present time, an important feature of operability is the presence or absence of involvement of the innominate or left common carotid artery. Aneurysms of the distal part of the aortic arch and the descending aorta can be managed by resection and grafting, while saccular aneurysms of the ascending aorta can be controlled by lateral excision and aortorrhaphy. Attempts at excision and grafting of fusiform aneurysms of the ascending aorta have until recently met with failure. The only successful case of resection of the ascending aorta is that of Cooley and DeBakey (6). In the

operation on this patient a mechanical pump-oxygenator was used. Lesions in this location pose a serious technical problem to the surgeon and probably should be operated on at present only under unusually favorable circumstances.

It has not been clearly established whether or not it is safe to excise the entire descending thoracic aorta. Even with hypothermia there is an increased risk of ischemic damage to the spinal cord, because of necessity all intercostal arteries must be sacrificed. The 2 patients in this series with aneurysms of this magnitude failed to survive operation, but satisfactory function of the lower extremities was evident in one patient who regained consciousness postoperatively. Such an extensive resection should probably be carried out only in the presence of pressing indications such as severe pain, hemoptysis, esophageal obstruction, and the like.

Excision of the diseased portion of the aorta followed by insertion of a graft is preferable to lateral excision and aortorrhaphy. This fact is apparent from our one experience with the latter technique which was followed by a recurrence and fatal rupture. DeBakey and Cooley have also had a recurrence after employing this method.

Resection and grafting require cross clamping of the aorta with its attendant difficulties. The limiting time of thoracic aortic occlusion is determined by the risk of damage to the spinal cord. Another hazard of cross clamping the aorta, particularly in its proximal portion, is the added burden placed on the heart. There is a wide and unpredictable variation in the time that the thoracic aorta may be occluded safely in the absence of coarctation of the aorta, the time varying from 18 to 45 minutes. Adams and van Geertruyden have conducted an exhaustive survey of this problem and their report is extremely pertinent to this subject. Because of dangers already mentioned, various protective measures have been suggested, including hypothermia and temporary internal and external shunts as well as permanent external shunts.

Our experience with a temporary external shunt is limited to 1 case. In this case disease of the aorta, to which the proximal end of the shunt was attached, led to serious hemorrhage and death soon after operation. This method, then, is not without hazard. Another disadvantage is the added time required for the operation to be completed. One reported patient operated upon with this technique was under anesthesia for 27 hours.

With the 1 exception just mentioned, all of our patients who underwent resection and grafting were operated on under hypothermia. For lesions arising below the eighth thoracic vertebra it is probably not necessary. This method is not without dangers. Ventricular fibrillation is a well known complication of hypothermia particularly in elderly patients with arteriosclerosis. Although the average body temperature achieved in our patients operated on by this method was less than 30 degrees C., a safer level would be 32 degrees C. This should allow up to an hour of aortic occlusion with minimal danger of spinal cord ischemia. The 1 patient in our group in whom weakness of the legs developed subsequent to operation underwent aortic occlusion for 90 minutes.

Another complicating feature of operations carried out under hypothermia is the temporary bleeding tendency that seems to occur fairly regularly with its use. The extensive dissection usually required for removal of thoracic aneurysms opens up a wide bed from which oozing may occur. Prompt and adequate replacement of blood often amounting to several liters is essential. This was not fulfilled in patient 4, who underwent excision of the entire descending thoracic aorta. He might otherwise have survived. Prompt and adequate rewarming is important and may be facilitated by irrigating the thoracic cavity with large quantities of warm saline solution prior to closure of the thorax.

The choice of grafting material is controversial. We have continued to employ

aortic homografts in the great majority of our patients undergoing aortic resection, regardless of the location. We have pursued this policy in expectation of the time when prosthetic materials will have proved their superiority. The problem in the thoracic aorta may be different from that in the abdominal aorta. Kanar and associates have shown experimentally that there is a greater tendency for homografts to undergo degenerative changes when inserted into the thoracic aorta than when placed in the abdominal aorta. For this reason it is quite possible that vascular prostheses may offer certain advantages over homografts in the treatment of thoracic aneurysms. Final proof of this supposition is lacking.

An additional technical point should be mentioned concerning the management of the sac of the aneurysm. Since hypothermia does impose a time limit on the safe performance of the procedure, blood flow should be re-established as soon as possible. This can be expedited in many instances by opening the aneurysm, removing clot and excess tissue, and suturing the graft in place before completely removing the sac. When blood flow has been re-established, there is a temptation to leave the sac undisturbed. Tuffier, Lam and Aram, and Bahnson (3) have all shown that such a decision may eventuate in the development of infection in the avascular remnant of the aneurysmal sac, with fatal results. The sac of the aneurysm should, therefore, be removed in each instance.

The over-all mortality rate in this small group of patients has been high, 33.3 per cent. Cooley and associates (7) have reported a similar mortality rate in 68 patients with thoracic aneurysm. We must ask ourselves if operations attended by a risk of this magnitude should continue to be performed. The poor prognosis of untreated patients with thoracic aneurysms compels us to attempt heroic measures in their behalf. Unquestionabiy as further experience is gained, the risk will decrease. All the deaths in our group of cases occurred in older people, the majority suffering from arteriosclerotic or syphilitic aneurysm. The consistently good results achieved in younger patients, particularly those with congenital, traumatic, or mycotic aneurysms, are clear evidence that such patients should be advised to undergo operation.

SUMMARY AND CONCLUSIONS

Aneurysms of the thoracic aorta are a serious threat to life, and surgical removal should be considered in their management. From surgical experience with 20 cases of thoracic aneurysms the following observations were made:

Arteriosclerotic aneurysms were the ones most commonly encountered. Others were syphilitic, traumatic, congenital, mycotic, and dissecting in nature.

Fifteen of the 20 aneurysms were removed and 10 of these patients survived resection, a mortality rate of 33.3 per cent. Grafts were employed in all but 1 patient, in whom lateral excision and aortorrhaphy were performed. Homologous aortic grafts were employed in 12 and polyvinyl formal (ivalon) grafts in 2 patients.

Hypothermia was used as a means of avoiding ischemia of the spinal cord during cross clamping of the aorta in most cases. Problems with its use, as well as other technical problems which are related to the performance of the operative procedure, are discussed.

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A ROENTGENOGRAPHIC STUDY OF THE LUMBOSACRAL SPINE IN CHILDREN

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THE FOLLOWING PRESENTATION is a corollary to studies which I began in 1943 and published in August 1953 (3) when the roentgenograms of 100 normal adults were compared with those of 100 adults with backache. In the present study the width of the lumbosacral disc and the angle of the sacrum were measured, and the incidence of structural alteration from the normal was determined in 100 children from 5 to 15 years of age (Fig. 2). This group consisted of 56 white and 44 colored children; 71 males and 29 females. These measurements were compared with the adult group to determine changes due to aging. The views were anteroposterior and lateral, with right and left oblique. The lateral view was made with legs fully extended to approximate the standing position. The width of the lumbosacral disc and the angle of the sacrum were plotted and measured on the lateral x-ray film (see Fig. 1).

RESULTS

The structural alterations from normal, including transitional vertebra, spina bifida occulta, spondyloschisis (spondylolysis), are shown in Table I. It should be noted particularly that spondylolisthesis was not found in this series of children. Spondyloschisis was found in 3 children, unilateral on the left in 2 and bilateral in 1.

The literature contains many references relating to the formation of spondylolisthesis and neural arch defects; however, the origin of these entities is still open to speculation. There seems to be increasing evidence that neural arch defects increase with age. Rowe and Roche, in an excellent article, reviewed the literature and reported on their study of roentgenograms, fetuses, and skeletons. In 100 x-ray films of normal children, they found 3 neural arch defects. They suggest, with appropriate reasoning, that the separate neural arch does not have a congenital origin, but is an acquired defect.

Failure of the two halves to unite, as in spina bifida, is congenital according to Stewart. He has also reported an increase of neural arch defects from 5 per cent at 6 years of age to 17 per cent at 30 years of age in Eskimo skeletons. He attributed this finding to postural stresses, a high accident rate, and more frequent occurrence of anomalous ossification. Hitchcock attributed neural arch defects to birth trauma, e.g., those produced by a position of acute flexion, and was able to produce such fractures in stillborn fetuses. This work has not been confirmed.

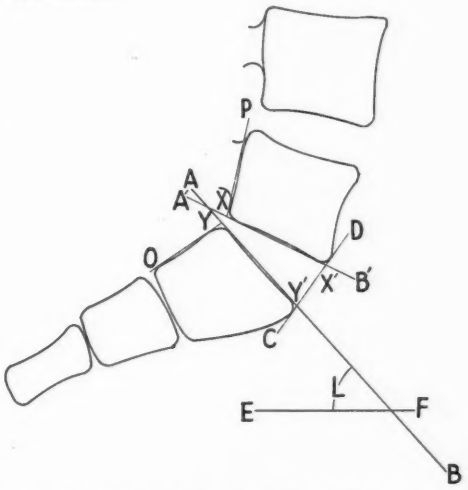

FIG. 1. Method of measuring angle L of sacrum, and width of lumbosacral disc.

From the Orthopedic Service of Children's Hospital of the East Bay, Oakland.

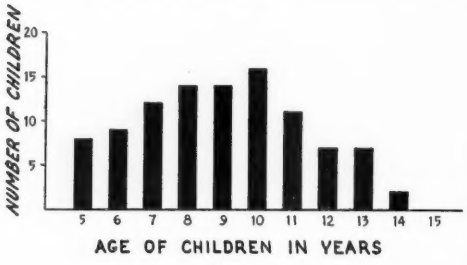

FIG. 2.

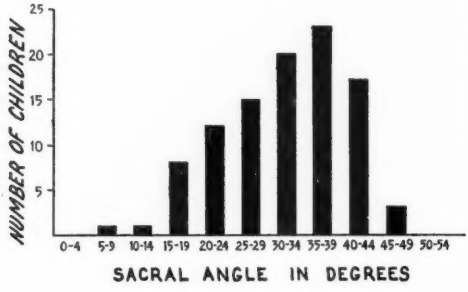

FIG. 4.

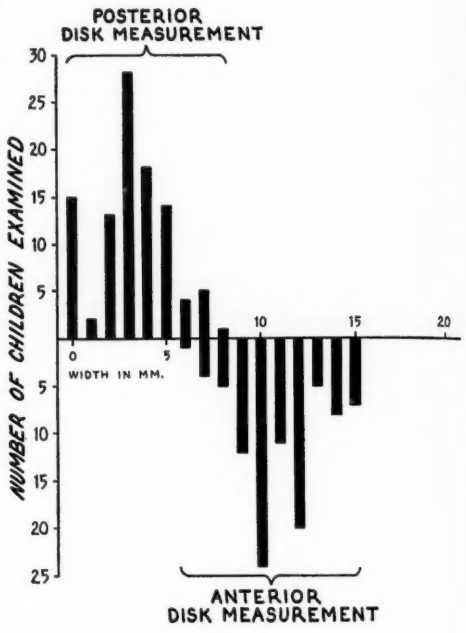

FIG. 3.

FIG. 2. Age incidence in group of 100 children.
FIG. 3. Width of fifth lumbar intervertebral disc in 100 normal children.
FIG. 4. Sacral angle of 100 normal children.

Likewise, it cannot be said that the slipping forward of the presacral vertebral body which occurs in spondylolisthesis is due either to trauma or to congenital defects. Both factors may be responsible. Since 1949, at Children's Hospital of the Easy Bay in Oakland, only 4 children with spondylolisthesis have been found in routine x-ray examination for other reasons.

TABLE I.—INCIDENCE OF CONGENITAL DEFECTS IN 100 NORMAL CHILDREN AGED 5 TO 15 YEARS

	No. of cases
Transitional vertebrae	
L 4	0
L 5	6
L 6	7
Butterfly process	4
Spina bifida occulta	
T 12 / L 1	1
L 4	0
L 5	10
L 6 or S 1	7
Spondylolisthesis	0
Spondyloschisis (spondylolysis)	
Left only	2
Right only	0
Bilateral	1

Transitional vertebrae were found in 13 children. This represented a change at the fifth or sixth (first sacral level) in which the body was incompletely developed or separated. To qualify as transitional, the transverse processes must have been markedly enlarged or articulated with the sacrum in close relation, pseudoarthrosis, or fusion.

WIDTH OF THE PRESACRAL DISC

The width or height of the presacral disc is of interest because of the frequency of roentgen interpretation of thin disc. Whenever a transitional vertebra was present in which the vertebral body was not completely separated, the first completely developed disc presumed to allow motion was measured. In 15 children, the posterior disc measured zero. The largest group of chil-

dren, numbering 28, had a disc measurement of 3 millimeters for the posterior, and a total of 64 children had an anterior disc measurement of from 9 to 12 millimeters (Fig. 3), approximating findings in adults.

THE SACRAL ANGLE

The angle formed by a line parallel to the superior surface of the sacrum and the horizontal was measured (Fig. 1). In the presence of a transitional vertebra, the surface of the lowest movable articulation was used. Seventeen children exhibited an angle of between 40 and 44 degrees, and 23 an angle of between 35 and 39, with a total of 63 children having an angle of 30 degrees or more (Fig. 4). The average angle for the entire group measures 31.6 degrees. As shown by Von Lackum, adults have an average sacral angle of 42.5 degrees.

SUMMARY AND CONCLUSIONS

Although this study represents a small group, it is of sufficient extent to indicate certain trends. It is significant that no spondylolisthesis was found in these normal children.

Spondyloschisis occurred in 3 per cent, in agreement with other authors. Of added interest is the fact that the general pattern of the width of the presacral intervertebral disc closely resembles that found in adults. The examination of the sacral angle reveals a similar over-all pattern, although there is a slightly less average sacral angle in children.

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PULMONARY RESECTION FOR TUBERCULOSIS IN CHILDREN

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THE INCREASING USE and apparent value of pulmonary resection in recent years as part of the treatment of pulmonary tuberculosis now seem to be well established. Our experience with this type of tuberculosis therapy at West Tennessee Tuberculosis Hospital has been reported (1). In the present article our experience with pulmonary resection for tuberculosis in children is presented.

During the period from January 1949 to April 1957, 193 children, less than 16 years of age, were admitted to the West Tennessee Tuberculosis Hospital with a diagnosis of pulmonary tuberculosis. Of these 193 children, 38 pulmonary resections were done in 34 patients. The results of resective therapy in this group of children compare favorably with results obtained in adults; indeed, the incidence of postoperative complications was quite low. While pulmonary resection for tuberculosis in children is done only occasionally, others have reported good results in small series of cases.

It is well known that in childhood most parenchymal lesions or primary tuberculosis are the result of bronchial obstruction by lymph nodes, and that most cases of primary tuberculosis clear after long term medical treatment. Walker, in a group of 578 cases of primary tuberculosis, found that resolution of an atelectatic area required about 2 years of medical treatment. Some parenchymal lesions clear after bronchoscopic removal of granulation tissue. If endobronchial disease is severe enough to produce irreversible bronchial stenosis or distortion, then, of course, the atelectatic area will not clear and may become the site of caseous lesions.

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In these 38 resections, no distinction was made clinically between primary tuberculosis and reinfection type of tuberculosis with regard to selection of patients for resective treatment. Indications for surgery were those generally used in selecting any patient for resection. For purposes of this report, the upper age limit was arbitrarily set at 15 years. In so doing, several children in the age group between 11 and 15 years had in all respects what appeared clinically to be reinfection not primary tuberculosis.

MATERIALS AND METHODS

In the 34 children under discussion, the diagnosis of pulmonary tuberculosis was based largely on the appearance of the chest film; confirmatory evidence included history of tuberculosis contact, positive skin test, and response to therapy. Only 16 patients (47 per cent) had positive sputa at the time of admission.

Length of illness prior to admission to the hospital (in some cases readmission for the second or third time), as obtained by history, varied from less than 6 months to between 48 and 60 months. Sixteen patients were ill less than 6 months prior to admission.

Treatment prior to resection consisted of: phrenic crush in 10 patients, pneumothorax in 3, pneumoperitoneum in 4, resection in 4, thoracoplasty in 1, bed rest in all patients, and chemotherapy in 31.

Collapse therapy in the form of phrenic crush, pneumothorax, pneumoperitoneum, thoracoplasty, or combinations of these was utilized in 17 patients; this type of treatment was carried out mainly during the first few years of this study when collapse therapy was more widely employed than it has been in recent years. Four children having bilat-

eral resections are shown as having prior resective therapy.

One patient had only 3 months' bed rest prior to resection. The majority had 6 months' bed rest, while a few patients had a year or more of bed rest before resection. Varying combinations of antituberculosis drugs were used throughout the course of therapy, both preoperatively and postoperatively, and consisted of: none in 3 cases, streptomycin only in 2, streptomycin and PAS in 15, isoniazid only in 2, isoniazid and streptomycin in 1, streptomycin, isoniazid, and PAS in 5, and isoniazid and PAS in 6. The various drugs and combination of drugs were administered or changed as dictated by intolerance to the drug, toxic reactions, ease of administration, favorable response to treatment, and susceptibility of the organisms. The majority of the patients received two or more drugs.

INDICATIONS FOR SURGERY

Children with well defined childhood tuberculosis who showed progressive improvement on medical management were not operated upon.

In the children of this study group, indications for resection were those employed in any patient with pulmonary tuberculosis, that is, destroyed lung, lobe, or segment in 24 instances; failure of previous collapse therapy in 3; and evidence of necrotic residual foci in 11.

In 3 patients, collapse therapy had failed, and, in addition, necrotic residual foci were present. The extent of resection consisted of: pneumonectomy in 2 cases, single lobe in 18, multiple lobes in 2, lobe and segment in 2, multiple lobes and segment in 1, segment in 11, and segments and multiple lobes in 2. Resections were about equally distributed between the two sides. In 22 resections, one or more lobes were removed; in 13 cases one or more segments were removed, and in 3 resections, both lobectomy and segmental resection were done. In most instances, the extent of the resection was confined to the removal of palpable disease.

TECHNIQUE

Very little needs to be said about the technique of pulmonary resection. However, a few important differences are encountered in children. As in all surgical procedures in children, the anatomical structures in the chest are small and delicate and must be handled with gentleness and care. It has been shown that with a skilled anesthetist present, children tolerate open thoracotomy quite well.

The amount of parenteral fluid administered during and after the surgical procedure must be judged carefully. Blood lost, determined fairly accurately by weighing sponges, must be replaced; saline is used sparingly, if at all. The pulmonary reserve in children is limited, and excessive use of saline can be disastrous. Fluid administration is usually confined to replacement of blood lost. Six to 12 hours after surgery most children can tolerate oral fluids with no difficulty. Retained secretions postoperatively usually present no special problem because of the rapid return of these young patients to normal activity.

PATHOLOGY

The character of the lesions encountered was anticipated by the appearance of the chest films and confirmed by examination of the surgical specimens. Each resected specimen was classified according to the type of major lesion found. In 11 cases cavities were the outstanding lesions; scattered fibronodular disease predominated in 15 cases; and 12 resected specimens revealed large caseous areas. In all cases varying degrees of all types of lesions were present. Bronchial stenosis seemed to have little effect on the type of parenchymal lesion found.

COMPLICATIONS

Thirty-one resections (81 per cent) were done without any postoperative complications. One death (2.6 per cent) occurred following the appearance of a bronchopleural fistula in a postpneumonectomy patient with extensive, far advanced, bilat-

eral tuberculosis. Bronchopleural fistula developed in 3 additional cases; 2 responded rapidly to closed intercostal drainage of the space, and the third patient required thoracoplasty for control of the space. Postoperative spread of tuberculosis occurred in 1 patient; however, at the time of discharge from the hospital, sputum was negative and the disease was considered to be inactive. Delayed expansion of the lung postoperatively without a demonstrable bronchopleural fistula occurred in 2 patients, both of whom recovered satisfactorily without further surgical intervention.

RESULTS

One patient, mentioned before, died following pneumonectomy for a totally destroyed lung. The remaining 33 patients showed excellent early results. They all had negative sputum, inactive disease, and were in excellent general health at the time of discharge from the hospital 3 to 6 months after resection. The 4 children who had bilateral resections similarly showed gratifying results. Long term follow-up studies are not yet available on all the patients in this group. The early results, however, are encouraging and support the feeling that there should be no hesitancy in extending pulmonary resection to the childhood and young adolescent age groups as part of the treatment of pulmonary tuberculosis.

SUMMARY

1. Thirty-eight pulmonary resections in 34 children, aged between 2 and 15 years, were done for pulmonary tuberculosis in the period from January 1949 to April 1957.

2. No distinction was made clinically between childhood and reinfection type of tuberculosis regarding selection for resection.

3. Indications for surgery in this group of children were those generally employed in selecting any tuberculosis patient for resective treatment.

4. The extent of resection was confined to the removal of palpable disease.

5. The types of resected lesions are described.

6. In 81 per cent (31 resections) there were no postoperative complications. One death occurred (postpneumonectomy bronchopleural fistula). Six additional complications occurred, but were successfully controlled.

7. Early results were excellent in 33 of 34 children who had pulmonary resections.

8. Pulmonary resection should be extended to the childhood and young adolescent age groups as part of the treatment of pulmonary tuberculosis.

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THE MANAGEMENT OF BLEEDING PEPTIC ULCER

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THE TREATMENT of continuing or recurrent massive hemorrhage from peptic ulcer is surgical. Since many patients stop bleeding spontaneously, the conservative management of actively bleeding ulcer is superior to surgery if it succeeds, as it does according to Todd in 75 per cent of patients; it fails, however, in 25 per cent. It is important to select those patients who run a risk of dying from hemorrhage under conservative treatment and to prepare them properly, so that if emergency operation is necessary, it can be performed with a minimum of risk.

The evaluation of treatment of reported series has been difficult in the past, because patients with minimal bleeding have been included or the correct cause of bleeding has frequently not been determined. Patients are considered to have had massive hemorrhage from peptic ulcer if a lowering of the total red cell mass below 60 per cent exists. An equivalent loss is believed to be represented by a sudden drop of the hemoglobin value below 8 grams with a visible blood loss of 1,000 cubic centimeters by emesis or melena or a need for more than 2,500 cubic centimeters of blood by transfusion in the first 48 hours after hemorrhage.

Sixty-one such patients were treated surgically at the Los Angeles County Harbor General Hospital, Torrance, California, from January 1952 through October 1954 (a 34 month period). Emergency operations were performed on patients who continued to bleed or in whom massive bleeding recurred after stabilization. Early elective operations were performed on patients whose bleeding had ceased, but whose history, such as a previous episode of hemorrhage, suggested that severe hemorrhage was likely to recur. These patients have been divided into two groups on a chronologic basis, each treated by a different method of preoperative management; the results of the two plans of management are compared. Plan A represents the method which had been used previously and had not proved entirely satisfactory, and plan B is a method introduced in an attempt to improve results.

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METHODS

Plan A was used to treat the first series of 29 patients over the initial 18 month period. According to this plan, the patients were first treated by the medical service; surgical consultation was requested only after it became evident that conservative treatment was not successful. Patients were given sufficient blood to avoid a state of clinical shock, were placed immediately on a feeding regimen, and only occasionally received emergency gastrointestinal roentgenologic studies.

Plan B was used to treat the second group of 32 patients during the final 16 months. Patients were followed from the time of their admission to the hospital by both the medical and surgical services. Sufficient blood was given to restore normal circulating red cell mass, the patients were placed on gastric suction immediately, and emergency gastrointestinal roentgenologic studies were performed. When emergency operation was not necessary and normal gastric emptying had returned, the patients were placed on a graduated feeding regimen.

Attempts were always made to obtain accurate histories. Sedatives (barbiturates) and antispasmotics (atropine or probanthine) were administered. If the history suggested that bleeding was probably from esophageal varices, a Sengstagen or Patton

bag was inserted to tamponade the varices, and suction was started. Rarely was esophagoscopy deemed necessary. When the bromsulphalein test showed less than 5 per cent retention, esophageal varices were never present. The blood was checked for derangement of the clotting mechanism (prothrombin time, bleeding, and clotting time).

The two plans of preoperative management are compared in Table I.

The two groups were similar in age and sex, severity of hemorrhage, and site of bleeding. Many of these patients were elderly, indigent, and poor risks. The mean age was 65 years with 26 per cent over the age of 70 years and 10 per cent in the 20 to 29 year age group. There were 40 males and 21 females, which is a much higher proportion of serious bleeding peptic ulcers in females than is usually reported. The sites of bleeding were: duodenal ulcer, 36; gastric ulcer, 17; marginal ulcer, 3; gastritis, 3; ulceration of a polypoid carcinoid of the stomach, 1; and ulceration of aberrant pancreas in the duodenum, 1. In no instance was massive hemorrhage related to gastric carcinoma. Patients with bleeding from esophageal varices are not included in this group.

RESULTS

1. Transfusion by the method used under plan B proved more satisfactory.

Patients requiring emergency operation and transfusion under plan A, who received only sufficient transfusion to keep them out of a state of clinical shock, were often found to have very unstable blood pressures and actually to be in a state of incipient shock because of a contracted circulating blood volume. By contrast, patients requiring emergency operation transfused under plan B, who received sufficient transfusion to restore normal circulating blood volume, were found to have stable blood pressures and tolerated the operative procedure much better.

Transfusion under plan B did not increase the amount of blood required. The total number of transfusions used in both methods averaged approximately the same; 14 per patient by plan A and 15 per patient by plan B. The transfusions in plan B, however, were administered in larger amounts earlier.

Transfusion by the method used in plan B, by which attempt is made to restore normal circulating blood volume, did not cause an increased incidence of continued or recurrent hemorrhage. Continued or recurrent hemorrhage occurred in 18 of 29 patients transfused by plan A (62 per cent) as compared to 15 of 32 patients transfused under plan B (47 per cent).

Transfusions to restore normal circulating blood volume are no more likely to cause congestive heart failure than transfusions sufficient to keep a patient out of shock. In 5 of the 29 patients transfused under plan A congestive heart failure developed and in 5 of the 32 patients transfused under plan B congestive heart failure also developed. These 10 patients responded to rapid digitalization and were operated upon. Two of these patients died postoperatively, both prepared under plan A. One patient, a 68 year old male, was operated upon at an emergency procedure, recurrent congestive failure developed on the seventh postoperative day, and he died. The other patient, a 72 year old male, was operated on at an early urgent procedure and died of a coronary occlusion on the fifth postoperative day. The other 8 patients with congestive heart failure had no further cardiac difficulty during the operative or postoperative periods.

The healing of incisions appeared to be better in patients transfused under plan B. There were 2 wound dehiscences in patients transfused under plan A and none among patients transfused under plan B.

2. Gastric suction as used under plan B proved to be much better preparation than immediate feeding as used in plan A.

Satisfactory emergency gastrointestinal series is almost impossible to perform in a dilated stomach filled with blood clot and food, the condition frequently found when patients with bleeding peptic ulcer are im-

mediately placed on a feeding regimen. Gastric suction proved very effective for emptying the stomach and permitting it to regain its tone so that satisfactory gastrointestinal series could be performed.

Patients treated by a feeding regimen and who required emergency surgery were frequently found to have gastric retention with tremendous dilation. As a result, the operative procedure was prolonged or made more difficult. By contrast, patients treated with immediate suction had stomachs that were empty, contracted, and better prepared for emergency operation.

The incidence of continued or massive recurrent bleeding due to peptic ulcer was lower in patients treated by gastric suction than in those treated initially by a feeding regimen. Continued or recurrent bleeding of such severity as to require emergency operation occurred in 18 of 29 patients (62 per cent) treated initially with a feeding regimen as compared to 15 of 32 patients (47 per cent) treated initially by gastric suction.

3. Emergency gastrointestinal roentgenologic studies proved very effective in localizing the bleeding point. Thirty-nine emergency gastrointestinal roentgenologic studies were performed. The radiographic diagnosis agreed with the operative finds in 35 cases, an accuracy of 90 per cent. In no instance was a patient operated upon for bleeding peptic ulcer and found to be bleeding from esophageal varices.

The gastrointestinal studies by the Hampton nonpalpation technique did not cause recurrence of bleeding. In only 1 patient did bleeding recur shortly after the series had ended. This was believed to have been no more than a chance occurrence. Emergency operation was necessary in 14 of 22 patients who did not receive emergency gastrointestinal series (68 per cent) as compared to 18 of 39 patients who did (46 per cent). Both groups are believed to have been composed of patients with bleeding ulcers of similar severity. It is possible that barium may have a beneficial effect in stopping hemorrhage or decreasing its incidence of recurrence.

TABLE I.—COMPARISON OF THE TWO PLANS OF PREOPERATIVE MANAGEMENT

	Plan A	*Plan B*
1. Responsible physician	The medical physician, the surgeon being called in consultation when it is evident that medical treatment has not been successful	Medical physician and surgeon in close co-operation from the start of treatment
2. Method of transfusion	Sufficient transfusion to keep patient out of a state of clinical shock	Transfusion rapidly, with restoration of normal circulating blood volume as the objective, using caution in patients suspected of having limited cardiac reserve
3. Preparation of the stomach	Immediately placed on a feeding regimen	Immediate evacuation and continuous suction of the stomach with a No. 16 or larger Levin tube
4. Localization of the bleeding point	Only rarely were emergency upper gastrointestinal series performed	Emergency upper gastrointestinal series using the Hampton nonpalpation technique performed as soon as the patient was out of shock and stabilized, even in the presence of slight continued bleeding
5. If emergency operation not necessary	Feeding regimen continued	Patient placed on graduated feeding regimen, after the return of normal gastrointestinal function

4. Massive upper gastrointestinal bleeding may be related to derangement of the clotting mechanism; this possibility should always be considered and investigated early by appropriate laboratory studies.

In 1 patient, bleeding was believed to be related to derangement of the clotting mechanism. This patient, a 28 year old male, was operated upon at an outside hospital for massive hematemesis. At operation no ulcer was found; only prominent rugae and diffuse ooze from the entire gastric mucosa could be seen. A partial gastrectomy was performed. The patient continued to bleed and was transferred to Harbor Gen-

eral Hospital where he was again transfused. When his prothrombin time was reported as 20 per cent, vitamin K oxide was administered; his prothrombin time then rose to 100 per cent and his bleeding stopped. Two direct transfusions were given. He has had no subsequent bleeding.

5. Comparison of the effect of the two plans of management revealed the following:

Emergency operation was necessary in 18 of 29 patients managed under plan A (62 per cent) as compared to 15 of 32 patients managed under plan B (47 per cent). The lower incidence of emergency operation among patients prepared under plan B is definitely believed to be related to the better method of preparation of the patient.

Emergency operations were performed on patients prepared under plan A at an average time of 72 hours after admission or after the first recurrent bleeding episode as compared to 36 hours for patients prepared under plan B. The earlier performance of emergency operation in the patients prepared under plan B is also definitely believed to be related to more satisfactory management which enabled a definite decision to be made with greater dispatch.

Among patients operated upon at emergency procedures, there were 18 prepared under plan A with 5 deaths—a mortality of 28 per cent—and 15 prepared under plan B with 1 death—a mortality of 7 per cent. Among the patients operated upon at urgent elective procedures, there were 11 prepared under plan A with 1 death—a mortality of 9 per cent—and 17 prepared under plan B with no deaths—a 0 per cent mortality. The age, sex, site of bleeding, and final cause of death are outlined in Table II. All deaths occurred in elderly patients, although the bleeding was no more severe in this group.

The deaths among the patients prepared under plan A are definitely believed to be related to less satisfactory preoperative preparation: (1) delay in reaching a decision as to which patients required emergency operation; (2) less adequate transfusion; (3) prolongation of the operation due to delay in localization of bleeding point and difficulty in management of a distended, filled stomach; and (4) higher incidence of emergency procedures in patients who had already been subject to considerable stress.

Only 1 death occurred among patients included under plan B. This patient was not actually managed by this method. It was attempted but not found possible. The patient who had massive hematemesis, was never really out of shock in spite of 19 transfusions in 36 hours, plus levophed. Gastric suction was not possible because of recurrent massive hemorrhage and shock. A Sengstagen bag was ineffective in controlling the hemorrhage. The patient was finally operated upon at the insistence of his physicians, who thought that death was certain if the bleeding was not stopped surgically. During the operation the patient received continuous rapid transfusion into 3 extremities, plus 3 pints of blood administered directly into the aorta after the abdomen was opened. The bleeding point was localized at the site of a marginal ulcer in a previous gastrojejunostomy and controlled, but shock was irreversible, and he died at the end of the procedure. This is an example of the type of case in which bleeding is so severe and the condition of the patient so deteriorated that no method of management will succeed.

DISCUSSION

Meulengracht believed that surgical intervention had little or no place in the treatment of bleeding ulcer. He reported a mortality rate of 1.5 per cent in 1,031 patients treated by his feeding regimen without operation. He included, however, all patients with any visible hematemesis or melena and admitted that in a few cases surgery might have been lifesaving. In our first group of 29 patients treated by a feeding regimen, there were 14 who had continued or recurrent bleeding of such severity that emergency operation to control the bleeding was thought necessary to save the patient's life.

At the other extreme, Stewart (20) advocated rapid evaluation, immediate replacement of blood, and emergency subtotal gastrectomy within 24 hours of admission. Operation was not delayed but carried on during blood replacement. The plan was based on the idea that it is impossible to tell which patients will survive better on a nonsurgical regimen. He reported a mortality of 10.7 per cent in 65 patients treated surgically as compared to a mortality of 21.4 per cent in 42 patients who refused operations. Among his patients believed to have had bleeding from peptic ulcer and operated upon in an immediate emergency operation, there were 5 errors in diagnosis. Welch pointed out that Stewart's method of rapid evaluation, replacement of blood and emergency operation at any hour of the day or night in the hands of less experienced surgeons would lead to many erroneous diagnoses and relatively high mortality.

If conservative medical management is adopted as the routine treatment of massive bleeding from peptic ulcer, there will be some patients who will die without surgical intervention, whereas a fair proportion could be saved by early indicated operation. If surgery is used only when medical treatment fails, the condition of the patient will have so deteriorated that the mortality will be very high. If emergency surgery is adopted as the routine treatment, some unnecessary operations will be performed and some will be performed that might better have been done later as elective procedures with a lower mortality.

Our plan of management consists of transfusion to restore normal circulating blood volume, gastric suction to empty the stomach, and emergency gastrointestinal series to localize the bleeding point, and emergency operation on those patients who continue to bleed or have a recurrence of bleeding while under treatment, preferably within 48 hours of onset. Those patients who stop bleeding, but whose past history, such as a previous episode of hemorrhage, suggests that recurrent bleeding is likely to occur, are operated upon as an early elective procedure after feeding and good preparation. We believe that the over-all mortality rate will be much lower with careful selection of the proper method of treatment for each patient.

TABLE II.—MORTALITY IN PATIENTS TREATED SURGICALLY FOR MASSIVE BLEEDING FROM PEPTIC ULCER

Patient	*Age*	*Sex*	*Site of bleeding*	*Cause of death*
PLAN A				
1. W.R.	53	M	Duodenal ulcer	Irreversible shock 36 hours postoperatively
2. A.H.	72	M	Duodenal ulcer	Died 12 hours postoperatively of cirrhosis and focal myocarditis
3. G.D.	72	F	Duodenal ulcer	Coronary occlusion on 5th postoperative day
4. R.B.	70	M	Duodenal ulcer	Bronchopneumonia and cardiac failure on 18th postoperative day
5. C.B.	68	M	Duodenal ulcer	Postoperative abdominal distention, left heart failure, persistent oliguria, and dehiscence on 10th day, with death after closure
6. G.B.	63	M	Marginal ulcer	Volvulus of small bowel around the gastroenterostomy, derotated, developed small bowel fistula, and died of bronchopneumonia
PLAN B				
7. A.D.	63	M	Marginal ulcer	Irreversible shock, starting preoperatively

The most important factor in determining the risk of mortality in patients with massive hemorrhage due to peptic ulcer is the severity and rapidity of bleeding and the adequacy of replacement. Stewart (21) pointed out that these patients die of anoxia of hemorrhage, and that the longer it goes uncorrected, the greater the danger. Atik and Simeone noted that elderly patients suffer progressive damage with repeated episodes of hypotension due to hemorrhage. Holloway and associates stated that when massive bleeding is inadequately treated, shock may become irreversible and vigorous late attempts at replacement of blood may precipitate cardiac failure.

The best immediate guides to the adequacy of transfusion therapy in hemorrhage

have been clinical observations on blood pressure, pulse, and other manifestations of shock, as well as on the adequacy of urinary output with an inlying catheter. Hemoglobin and hematocrit determinations are valuable aids, but tend to lag behind the clinical course of the patient. There is an early disparity between the concentration and circulating quantity of hemoglobin which becomes apparent as hemodilution progressed during the first 24 to 48 hours. Stewart (22) and Gunz both used the method of Gregersen, with Evans blue dye, to determine plasma volume; then from the plasma volume and hematocrit they calculated the total blood volume; and last they determined the total circulating red cell mass by the difference between plasma volume and total blood volume. They believed that the total red cell mass was the important determination in evaluating the condition of the patient. The deficit of red cell mass was determined by comparison with established standard values for the normal body weight of the patient and replacement requirement was computed, assuming that each pint of blood contains 200 to 220 cubic centimeters of red cells. We performed blood volume studies, using the Evans blue dye method, on several patients, but did not find it practical in routinely following the clinical course of patients with hemorrhage because with the laboratory facilities available, we were unable to reproduce accurate results regularly or obtain this determination during the night shift when many of these patients were first seen. In most patients we roughly estimated the replacement requirement by using the hemoglobin determinations and administering 1 transfusion for every gram of hemoglobin below normal. The adequacy of replacement therapy was determined by a combination of clinical observations with serial hemoglobin and hematocrit determinations performed every 4 to 6 hours, until hemoglobin was restored to 14 grams and hematocrit to 40 per cent. This method proved satisfactory in the actual management of patients, although when accurate blood volume studies are readily available the deficit may be more definitely determined by this means.

In the treatment of bleeding there is no substitute for whole blood. Transfusions should be started immediately and continued until the normal circulating red cell mass is restored. The rapidity of transfusion should always be consistent with the evaluation of the cardiac status of the patient; care should be used in any patient with marginal cardiac reserve. Our own experience, as well as that of many others, indicates that this method of transfusion does not increase the recurrence of bleeding. It prevents death from exsanguination, relieves hemorrhagic shock, prevents damage from anoxemia to such vital organs as the brain, liver, and kidneys, and prepares the patients to withstand the rigors of an emergency operation if continued or recurrent hemorrhage requires it.

Rudman and Stewart (19) reported that despite the large quantities of blood transfused, none of their patients showed evidence of cardiac embarrassment, neither those with cardiac disease nor those in the older age group. This observation differs from our experience in which 10 patients developed congestive failure while being transfused. The higher incidence of cardiac failure among our patients is probably due to the fact that we were treating an older age group; 65 years was the mean age of these patients.

Anemia persists in patients who do not receive sufficient transfusion to restore normal circulating red cell mass. In the presence of anemia the healing of wounds is retarded, for the manufacture of hemoglobin has first priority on available protein. Whipple and associates (25, 26) showed by animal experiments that there is a selective replacement of specific body protein by which hemoglobin has priority over tissue protein. Lyons and Mayerson stated that persistent transfusion to restore normal red cell mass so that healing will not be retarded is very important for patients who require surgery for massive bleeding from peptic ulcer.

Immediate gastric suction is not offered as a substitute for feeding. Food can only neutralize acid-peptic secretion by contact with it. Most of these patients have functional or organic obstruction of gastric emptying, and early feeding causes tremendous dilation of the stomach with blood clot and undigested food. With dilatation, motility is lost, food is not brought into contact with acid-peptic secretions, inadequate neutralization occurs, and the ulcer may progress. Gastric retention and dilatation is apt to produce nausea, often with severe emesis. Rafsky and Weingarten abandoned Meulengracht's method of feeding because persistent vomiting occurred in a third of the patients so treated. Holman pointed out that when the patient is nauseated feeding may initiate vomiting, dislodge thrombi, and contribute to the recurrence of bleeding. With gastric retention a satisfactory gastrointestinal series is impossible and an exploratory operation made difficult. Gastric suction proved very effective in removing blood clot and residual food, thus permitting the stomach to contract and regain its normal tone. It removes acid-peptic juice effectively, which if left, may cause increase in the activity of the ulcer. It assists in the evaluation of the activity of bleeding, and satisfactorily prepares the stomach for an early adequate gastrointestinal series. It produces an empty, contracted stomach which makes an operative procedure easier, should emergency operation be required.

The emergency gastrointestinal series, which should be performed as soon as the patient has restoration of normal circulating blood volume and evacuation of the stomach by gastric suction, is important to localize the bleeding point; since, if hemorrhage should continue or recur, an emergency operation to control the bleeding and prevent exsanguination may be performed with greater accuracy and dispatch. In our series the accuracy of the x-ray diagnosis in emergency gastrointestinal series, using the Hampton nonpalpation technique, was 90 per cent. Welch reported an 85 per cent accuracy, Knowles and associates an 86 per cent accuracy, and Alsobrook and associates a 92 per cent accuracy, indicating that the procedure was of real value. Baker reported that gastrointestinal series performed at least 3 weeks after bleeding demonstrated the ulcer in only 43 per cent of the cases. Zinninger stated that barium studies using the Hampton technique had caused no harm, and on several occasions bleeding ceased after the barium study. This experience is similar to our own.

We have attempted, when possible, to decide within 48 hours, which patient will require emergency operation, for even with adequate transfusion the condition of the patient deteriorates with continued hemorrhage.

For our patients prepared under plan B there was close co-operation between the medical and surgical services during the entire course of the patient's care. Dunphy and Hoerr stated that the surgeon should not be called in at the last minute to perform a heroic procedure upon a nearly moribund patient. Ferguson has pointed out that with close medicosurgical co-operation, the charge that the patient has been left too late for surgery can be avoided.

The operation of choice in these cases is partial gastrectomy, with removal of the ulcer where possible and combined with vagotomy when indicated. As pointed out by Heuer, Baker, and Allen and Oberhelman ligation of the bleeding point is not a reliable procedure and gives a fairly high incidence of recurrent bleeding. Baker reported that recurrent bleeding occurred in 4 out of 5 patients in whom ligation was performed. Albright and Kerr, who advocate multiple figure-of-8 sutures of the ulcer bed, reported that in 7 patients on whom this procedure was used, 1 subsequently bled and died. The only patient in our series who had ligation of the bleeding point, treated under plan A, subsequently bled on the second postoperative day. Bohrod believed that ligation of the vessels outside the duodenum is futile as there are too many

anastomosing vessels. Two other patients, prepared under plan A., had vagotomy and pylorplasty performed without subsequent bleeding. Recurrent hemorrhage occurring after this procedure, however, has been reported by many surgeons.

CONCLUSIONS

The best management of massive bleeding from peptic ulcer requires close co-operation between the medical and surgical services. While patients with minimal bleeding from ulcer can be treated satisfactorily by a feeding regimen, antacids, sedatives, antispasmotics, and occasionally by transfusion, more massive or recurrent bleeders, who may require emergency operation, are not well prepared by this regimen. We believe that a policy of careful selection of the patients requiring emergency operation will give the lowest mortality. Patients who continue to bleed or who have a massive recurrence of bleeding should have an emergency operation before their condition deteriorates. If managed by plan B they will have restoration of normal circulating red cell mass, and incipient shock will be avoided; they will have a relatively empty contracted stomach, and the bleeding point will be localized so that operation may be performed without unnecessary delay. The patient whose bleeding stops but whose past history suggests that severe recurrent bleeding is likely to occur, can be operated upon at an early urgent procedure with good preparation and almost no mortality.

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REOPERATION AFTER RESUSCITATION FROM CARDIAC ARREST

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DURING THE YEARS 1949 to 1956, there have been 28 patients operated upon after successful cardiac resuscitation at the Presbyterian and Memorial Hospitals of New York City. These patients have undergone a total of 42 subsequent operations. A study of this group was suggested by the need to gain more precise prognostic information as to whether or when operation might be undertaken with reasonable safety after revival from cardiac arrest.

The operation may be needed to correct the original disease or for unrelated conditions. The patient whose heart has been resuscitated raises at least five questions: (1) How soon after the cardiac arrest can the operation be performed safely if the surgical indications are urgent? (2) How can the causes of the arrest be avoided during the second operation? (3) What is a safe anesthetic agent or method? (4) What medical preparation is necessary for the resuscitated heart prior to another anesthetic and operation? (5) What is the possibility of the occurrence of another cardiac arrest?

In this series the patients ranged from 2 months to 73 years of age. Twenty-three of the patients were over 40 years of age and 11 were in their seventh decade. There were 14 males and 14 females in this series. Cardiac arrest occurred during induction of anesthesia in 12 cases, during the operation in 11 cases, immediately postoperatively in 4 cases, and in 1 case during the positioning of the patient between induction and operation. Fifteen different surgical procedures were contemplated, being performed or just completed when the cardiac arrest occurred (Table I).

The probable causes of the cardiac arrests were inadequately treated hemorrhage in 5 cases, overdose of anesthetic agent (general, topical, or regional) in 11 cases, hypoxia or asphyxia in 6 cases, myocardial infarction in 1 case, the result of a cardiocirculatory reflex in 3 cases, hypothermia in 1 case, and the cause could not be determined in the remaining case.

In all 28 of the cases of cardiac arrest, thoracotomy was performed. Cardiac massage alone reinstituted the cardiac action in 21 of the cases. Three patients received procaine hydrochloride, epinephrine, or calcium chloride into the heart in addition to the cardiac massage. Two patients were given rapid blood replacement, and in 1 case of ventricular fibrillation the use of the electrical defibrillator was required.

There were 7 different combinations of drugs given for preanesthetic medication to the 28 patients in whom cardiac arrest occurred (Table II). Two of the patients received no premedication, 7 had atropine, and 19 had scopolamine.

Sixteen different anesthetic combinations (Table III) were utilized of which 3 were regional or local and 25 were general anesthesia; in 17 of these cases endotracheal intubation was used (Table V). Four of the patients had only 1 anesthetic agent throughout. Of the remaining patients, 22 received thiopental at some time, 18 received ether, 4 received cyclopropane, and 9 patients had a muscle relaxant.

Fourteen of the subsequent operations oc-

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TABLE I.—OPERATION DURING WHICH CARDIAC ARREST OCCURRED

	No. of cases
Hysterectomy	1
Hysterectomy and node dissection	1
Pelvic exenteration	1
Gastrectomy	1
Bowel resection	1
Hepatectomy, partial	1
Thoracotomy	2
Thoracolumbar sympathectomy	1
Repair cleft lip	1
Ligation carotid artery	1
Radical neck dissection	2
Craniotomy	2
Total	15
Operation not performed	13
Total	28

TABLE II.—PREMEDICATION

	No. of arrest operations	*No. of subsequent operations*
Atropine	—	4
Barbiturate	—	1
Barbiturate+atropine	—	4
Barbiturate+scopolamine	—	4
Meperidine+atropine	6	5
Meperidine+scopolamine	13	16
Morphine+atropine	1	1
Morphine+scopolamine	4	4
Barbiturate+meperidine+scopolamine	1	—
Barbiturate+morphine+scopolamine	1	—
Morphine	—	1
None	2	2
	28	42

curred within 1 month after the arrest. The times varied from 1 to 25 days with 9 of the patients being reoperated upon within 2 weeks. The remaining 28 operations occurred from 1 month to 3 years and 5 months later. Of these, 9 patients were reoperated upon within the following 9 months.

For the succeeding 42 operations after the cardiac arrest, 10 different combinations of drugs were given for preanesthetic medication. There was no premedication in 2 cases, atropine in 10 cases, and scopolamine in 24 cases (Table II).

Seventeen anesthetic combinations (Table III) were used for the subsequent operations (Table IV). In 1 case no agent was used, in 11 cases regional or local, and in 30 cases general anesthesia, of which 17 were with endotracheal intubation. Fourteen patients had only 1 anesthetic agent throughout and the remainder received thiopental at some time in 23 cases, ether in 12, cyclopropane in 5, and 8 patients had a muscle relaxant (Table V).

The most common complication in the subsequent operations for various surgical procedures was the occurrence of hypotension in 7 patients. Six of these patients required vasopressors to maintain the blood pressure despite light anesthesia and 1 patient required the administration of blood to compensate for blood loss. The only death occurred in a poor risk child who, after severe hemorrhage and cardiac asystole, did not respond to resuscitation methods.

DISCUSSION

In view of these data, one may have at least partial answers to the five previously stated questions.

1. Emergency operations must be performed at once after cardiac arrest if the patient is to survive. The 1 case in this series in which reoperation occurred within 1 day was of a patient who required a thyroidectomy to remove enough gland so that a tracheostomy might be carried out.

Reoperation for elective procedures may be considered analogous to the management of patients with varying degrees of myocardial ischemia subsequent to coronary occlusion.

Peddie and associates, in their report on the structural changes of the heart in 14 patients who died after cardiac massage, found that there was a traumatic, hemorrhagic pericardial effusion in 7 patients who died immediately, and in 1 who died after 6 hours. There was evidence of some damage to the myocardium and pericardium in all the patients in whom cardiac massage lasted more than 15 minutes.

It would appear from the cases in this series that, in patients in whom the arrest responded immediately to massage with little or no trauma to the myocardium, the subsequent operation may be performed with reasonable assurance of safety in 10 days to 2 weeks. Overdose of an anesthetic agent is an example of this situation.

TABLE III.—ANESTHETIC AGENTS USED

	No. of arrest operations	*No. of subsequent operations*
Local procaine or tetracaine or lidocaine hydrochloride	—	7
Spinal-dibucaine or tetracaine	—	3
Topical-tetracaine	2	1
None	—	1
Epidural-piperocaine hydrochloride	1	—
Open ether	1	2
Nitrous oxide-oxygen-ether	1	1
Cyclopropane-ether-oxygen	1	—
Cyclopropane-oxygen	—	2
Cyclopropane-ethylene-oxygen	—	1
Ether-oxygen-relaxant	—	1
Tribromethanol-topical-thiopental-nitrous oxide-oxygen	1	—
Thiopental-nitrous oxide-oxygen	1	7
Thiopental-nitrous oxide-oxygen-topical	2	5
Thiopental-nitrous oxide-oxygen-topical-relaxant	1	1
Thiopental-nitrous oxide-oxygen-ether	3	2
Thiopental-nitrous oxide-oxygen-ether-relaxant	5	4
Thiopental-ethylene-oxygen	1	—
Thiopental-ethylene-oxygen-relaxant	—	1
Thiopental-ethylene-oxygen-ether	1	1
Thiopental-cyclopropane-oxygen	1	1
Thiopental-cyclopropane-ether-oxygen	3	—
Thiopental-cyclopropane-ether-oxygen-relaxant	3	1
	28	42

TABLE IV.—SUBSEQUENT OPERATIONS AFTER CARDIAC RESUSCITATION

	No. of cases
Craniotomy	2
Repair cleft palate	1
Resection maxilla	1
Resection maxillary antrum	1
Thyroidectomy	1
T & A	1
Excision recurrence neck tumor	1
Tube pedicle chest	2
Excision breast tumor	1
Radical mastectomy	1
Thoraco-lumbar sympathectomy	3
Hepatectomy, partial	1
Gastrectomy	1
Excision recurrence abdominal wall	1
Revision of colostomy	1
Excision sigmoid polyp	1
Prostatectomy	1
Exploratory laparotomy	2
Excision rectal stump	2
Sigmoid resection	1
Repair vesical fistula	2
Bladder suspension	1
Nephrostomy	2
Hysterectomy	1
Pelvic exenteration	1
Removal of pelvic pack	1
Herniorrhaphy	4
Spinal column	2
Bronchoscopy	1
	42

Patients requiring a moderate amount of cardiac massage associated with minimal asphyxia may be reoperated upon in 2 to 4 weeks.

Patients who required prolonged massage, with prolonged hypoxia and evidence of myocardial damage, should be treated as though severe coronary occlusion had occurred and the operation be delayed for at least 3 months.

In patients with prolonged cardiac massage and borderline recovery of mental function, the safe period for reoperation may vary from 6 weeks to 6 months. Certainly, stability of cerebral and cardiovascular function should be achieved first.

2. Overdose of the anesthetic agent or asphyxia resulted in 12 arrests during the period of induction of anesthesia in this series. The prevention of cardiac arrest begins with the establishment of an adequate airway as induction begins. Anesthetic agents and methods must be used in a flexible fashion to compensate for variations in the patient's habitus, airway, and myocardial status. Stereotyped anesthetic sequence of agents and techniques with overdose and malventilation were responsible for more cardiac arrests than any other cause in this series.

The prevention of cardiac arrest from overdosage of agent requires the constant exercise of care. In these days of analgesia or light anesthesia with supplementation by relaxants, overdosage of anesthesia can be avoided and represents a significant advance in anesthetic safety, providing adequate ventilation is maintained.

TABLE V.—ANESTHETIC METHODS

	No. of arrest operations	*No. intubated*	*No. of subsequent operations*	*No. intubated*
Local or regional block	–		7	–
Epidural	1		–	–
Spinal	–		3	–
Topical	2		1	
Open drop	1		–	
Nonrebreathing	1	1	2	2
Semiclosed circle absorption circuit	6	5	14	8
Closed circle absorption circuit	17	11	14	8
None	–		1	
	28	17	42	18

TABLE VI.—SUMMARY OF CASES

Name Age Sex	*Operation*	*Pre-medication*	*Anesthesia*	*Time of arrest*	*Cause*	*Subsequent operation*	*Pre-medication*	*Anesthesia*
1. L.M. 72 M	Excision diverticulum, cancelled 9–20–49	Meperidine 75 mgm. Scopolamine 0.3 mgm.	Cyclopropane ether-O_2, intratracheal	End of induction	Overdose of ether	Esophageal diverticulum 12–19–49	Meperidine 75 mgm. Scopolamine 0.3 mgm.	0/15% tetracaine cervical block
2. R.D. 61 F	Excision sigmoid polyp, cancelled 3–21–50	Morphine 9 mgm. Scopolamine 0.4 mgm.	Thiopental-cyclopropane Ether-O_2	30 minutes after induction. Before skin prep.	Overdose of ether	Excision sigmoid polyp 5-15-50	Secobarbital 100 mgm. Scopolamine 0.4 mgm.	Nitrous-oxide-oxygen-ether
3. M.B. 38 N-F	Thyroidectomy, cancelled 4–24–50	Meperidine 100 mgm. Scopolamine 0.4 mgm.	2% tetracaine, topical	During instillation of topical anesthesia	Overdose of tetracaine	Emergency thyroidectomy and tracheotomy 4–25–50	Scopolamine 0.3 mgm. i.v.	Intubated awake Thiopental-nitrous-oxide-oxygen
4. W.W. 75 M	Rt. inguinal hernia, cancelled 6–5–50	Meperidine 50 mgm. Scopolamine 0.3 mgm.	1/5% piperocaine, epidural	33 minutes after injecting drug	Total spinal	Right inguinal hernia 6–16–50 Prostatectomy 6–28–50	Meperidine 50 mgm. scopolamine 0.3 mgm. Meperidine 50 mgm. scopolamine 0.3 mgm.	1% procaine local infiltration Cyclopropane-ether-oxygen curare
5. G.D. 2 mos. M	Bilateral cleft lip 7–14–50	None	Open ether	End of operation	Repeated anoxia	Repair cleft palate 7–17–53 3 yrs. old	Secobarbital 30 mgm. Scopolamine 0.2 mgm.	Ether intratracheal Nonrebreathing
6. M.T. 48 F	Parathyroid exploration 7–19–50	Meperidine 50 mgm. Scopolamine 0.3 mgm.	Thiopental induction Nitrous oxide, cyclopropane, ether-oxygen	Induction operation was then completed	Anoxia	Hysterectomy plus bilateral salpingo-oophorectomy 8–1–50	Meperidine 50 mgm. Scopolamine 0.3 mgm.	Cyclopropane-oxygen
7. B.C. 52 F	Right thoracolumbar sympathectomy cancelled 4–3–51	Meperidine 75 mgm. Scopolamine 0.4 mgm.	Nitrous-oxide, oxygen, ether	Induction	Overdose of ether	Right thoracolumber sympathectomy Left thoracolumbar sympathectomy 5–5–51	Pentobarbital 100 mgm. Scopolamine 0.3 mgm. Meperidine 50 mgm. Scopolamine 0.4 mgm.	Ethylene-ether-oxygen topical intratracheal Thiopental intratracheal cyclopropane oxygen, topical
8. J.S. 9 F	Topectomy 7–13–51	Morphine 7 mgm. Scopolamine 0.4 mgm.	Tribromethanol tetracaine topical. Intratracheal thiopental. Nitrous oxide, oxygen	Closing dura	Traction reflex dura	Bilateral frontal lobectomy 11–20–51	Morphine 7 mgm. Scopolamine 0.3 mgm.	Thiopental, nitrous-oxide, oxygen, intratracheal
9. O.M. 45 N-F	Craniotomy cancelled 10–8–51	Meperidine 100 mgm. Scopolamine 0.4 mgm.	Tetracaine topical, thiopental, nitrous oxide, oxygen intratracheal	Elevating cranial bone flap	Dural reflex	Craniotomy 10–19–51	Meperidine 100 mgm. Scopolamine 0.4 mgm.	Topical thiopental, nitrous-oxide, oxygen
10. J.K. 47 F	Right thoracolumbar sympathectomy 1–7–52	Meperidine 100 mgm. Scopolamine 0.4 mgm.	Thiopental intratracheal, ethylene, ether, oxygen	In transit to recovery room	Unknown	Left thoracolumbar sympathectomy 1–25–52	Meperidine 100 mgm. Scopolamine 0.4 mgm.	Ethylene cyclopropane, oxygen intratracheal

TABLE VI.—SUMMARY OF CASES—Continued

Name Age Sex	*Operation*	*Pre-medication*	*Anesthesia*	*Time of arrest*	*Cause*	*Subsequent operation*	*Pre-medication*	*Anesthesia*
11. M.P. 59 M	Gastrectomy 3–10–52	Meperidine 100 mgm. Scopolamine 0.4 mgm.	Cyclopropane, ether, oxygen, curare, Intra-tracheal	15 minutes after operation in recovery room	Asphyxia	Herniorrhaphy 1–9–53	Meperidine 100 mgm. Scopolamine 0.4 mgm.	Dibucaine spinal
12. W.K. 26 M	Postoperative repair of thoracic aorta 6–9–49	None	Thiopental, cyclopropane, oxygen, intratracheal	As chest was reopened	Hemorrhage	T&A 1950	Pentobarbital 100 mgm.	Local
13. W.B. 70 N-M	Hernia cancelled 4–23–53	Meperidine 75 mgm. Scopolamine 0.4 mgm.	Thiopental, ethylene, oxygen	During skin prep.	Thiopental overdose and anoxia	Revision of colostomy 9–14–55	Atropine 1.0 mgm.	Local infiltration 1% procaine
14. J.R. 26 mos. M	Resection hepatoma 12–28–54	Secobarbital 30 mgm. Morphine 2 mgm. Scopolamine 0.2 mgm.	Cyclopropane ether oxygen intubated Nitrous-oxide oxygen, ether nonrebreathing	While trying to institute hypothermia	Hypothermia	Resection of hepatoma 1–17–55	Secobarbital 40 mgm. Scopolamine 0.2 mgm.	Nitrous-oxide oxygen, ether vinethene nonrebreathing, controlled respiration. Patient died hemorrhage
15. E.S. 46 N-M	Ligation of left external carotid artery 7–17–53	Secobarbital 100 mgm. Meperidine 75 mgm. Scopolamine 0.4 mgm.	Thiopental, nitrous oxide cyclopropane ether oxygen. Induction for intubation. Thiopental nitrous oxide oxygen intratracheal	With ligation of left carotid artery	Unknown ? Carotid sinus reflex	Resection maxilla 8–1–53 Excision recurrent tumor left antrum 8–18–55 Herniorrhaphy 1–2–56	Meperidine 50 mgm. Scopolamine 0.5 mgm. Meperidine 75 mgm. Scopolamine 0.4 mgm. Morphine 10 mgm.	Thiopental, nitrous oxide, oxygen meperidine intubated Cocaine, topical 10%, thiopental, nitrous oxide, oxygen, succinylcholine, intubated 1% procaine, local + nitrous oxide, oxygen
16. M.L.A. 43 M	Débridement of decubitus ulcer and spinal fusion. Operation cancelled 2–3–54	Morphine 12 mgm. Scopolamine 0.4 mgm.	10% cocaine, topical, thiopental, nitrous oxide, oxygen, succinylcholine intubated	With positioning in prone position	Anoxia	Removal of plate and screws of spine 3–15–54 Débridement and graft of decubitus ulcer and excision of sinus tract of spine 7–8–54	Morphine 5 mgm. Scopolamine 0.4 mgm. Atropine 0.3 mgm.	Thiopental, nitrous oxide, oxygen, intubated Thiopental, meperidine, nitrous oxide, and oxygen
17. E.C. 63 M	Gastrectomy cancelled 10–7–53	Meperidine 75 mgm. Scopolamine 0.5 mgm.	Thiopental, nitrous oxide, oxygen, succinylcholine, intubated. Controlled cyclopropane, ether, oxygen	During induction	Ether overdose	Gastrectomy 11–20–53	Meperidine 75 mgm. Scopolamine 0.5 mgm.	Thiopental, ethylene, oxygen, succinylcholine, intubated

TABLE VI.—SUMMARY OF CASES—Continued

Name Age Sex	*Operation*	*Pre-medication*	*Anesthesia*	*Time of arrest*	*Cause*	*Subsequent operation*	*Pre-medication*	*Anesthesia*
18. D.B. 66 M	Exploratory thoracotomy	Morphine 10 mgm. Atropine 0.6 mgm.	Thiopental-succinylcholine-intubated ether-oxygen	During operation	Myocardial infarction preoperatively	Left inguinal herniorrhaphy 9–24–56	Phenobarbital 100 mgm. Atropine 0.3 mgm.	Tetracaine Spinal T-11
19. T.P. 59 M	Right radical neck and mandible resection 12–14–54	Demerol 75 mgm. Scopolamine 0.4 mgm.	Thiopental, nitrous oxide, oxygen and ether, intubated	During operation	Hemorrhage and tension pneumothorax	Construction of chest tube pedicle 1–14–55	Phenobarbital 60 mgm. Atropine 0.4 mgm.	Thiopental, nitrous oxide and oxygen
						Migration of tube 7–12–55	Demerol 75 mgm. Atropine 0.4 mgm.	1% lidocaine local
						Bronchoscopy 8–16–55	Demerol 75 mgm. Atropine 0.4 mgm.	2% tetracaine
20. I.L. 71 F	Radical mastectomy cancelled 11–9–53	Demerol 50 mgm. Atropine 0.4 mgm.	Nitrous oxide, oxygen and ether	During induction	Ether overdose	Radical mastectomy 11–24–53	Demerol 50 mgm. atropine 0.4 mgm.	Thiopental, nitrous oxide and oxygen
21. E.P. 56 F	Hysterectomy and appendectomy 9–28–56	Demerol 75 mgm. Scopolamine 0.3 mgm.	Thiopental, succinylcholine-intubated ether-O_2	During operation	Hemorrhage	Repair vesical fistula 10–23–56	Morphine 8 mgm. atropine 0.4 mgm.	Thiopental, nitrous oxide and oxygen
						Bilateral nephrostomies 10–23–56	Morphine 8 mgm. Scopolamine 0.4 mgm.	Thiopental, nitrous oxide and oxygen
22. G.L. 65 M	Gastroscopy cancelled 12–3–53	Phenobarbital 120 mgm. Demerol 50 mgm. Atropine 0.4 mgm.	1% tetracaine topical (3 c.c.)	Convulsions during topical	Tetracaine toxicity	Exploratory laparotomy 12–28–53	Atropine 0.4 mgm.	Thiopental, succinylcholine-intubated-ether, oxygen
23. A.M. 54 M	Left radical neck dissection 9–24–54	Demerol 75 mgm. Scopolamine 0.4 mgm.	Thiamylal, nitrous oxide and oxygen-intubated	With application of neck dressing	Carotid sinus reflex	Excision recurrent tumor left neck 4–6–56	Demerol 75 mgm. Atropine 0.5 mgm.	None (denervated area)
24. R.B. 61 F	Hysterectomy and pelvic node dissection	Demerol 100 mgm. Atropine 0.4 mgm.	Thiopental, succinylcholine, intubated, ether-O_2	During operation	Hemorrhage (19 pts. of blood in 2 hrs.)	Removal of abdominal pack 1–16–54	None	Thiopental
						Left nephrostomy 1–11–55	Phenobarbital 90 mgm. Atropine 0.4 mgm.	Thiopental, nitrous oxide, oxygen and ether-intubated
						Repair vesicovaginal fistula 2–8–55	Demerol 75 mgm. Atropine 0.4 mgm.	Ether-oxygen-curare intubated
						Pelvic exenteration 3–13–57	Demerol 50 mgm. Scopolamine 0.4 mgm.	Thiopental-succinylcholine intubated
						Excision of rectal stump 4–10–57	Demerol 75 mgm. Scopolamine 0.4 mgm.	Thiopental-nitrous oxide-oxygen-ether, succinylcholine intubated

TABLE VI.—SUMMARY OF CASES—Continued

Name Age Sex	*Operation*	*Pre-medication*	*Anesthesia*	*Time of arrest*	*Cause*	*Subsequent operation*	*Pre-medication*	*Anesthesia*
25. J.D. 73 F	Exploratory laparotomy cancelled 8–18–54	Demerol 50 mgm. Atropine 0.3 mgm.	Thiamylal-nitrous oxide, oxygen and ether intubated	During induction of anesthesia	Ether overdose	Exploratory laparotomy 9–2–54	Morphine 8 mgm. Scopolamine 0.4 mgm.	Cyclopropane oxygen
26. J.A. 51 F	Pelvic exenteration 5–8–54	Demerol 75 mgm. Atropine 0.4 mgm.	Thiopental, succinylcholine, intubated, ether-O_2	During operation	Hemorrhage, 3,500 c.c. of blood in 40 min.	Excision recurrent ca of abdominal wall	Pentobarbital 90 mgm. Scopolamine 0.4 mgm.	Thiopental, nitrous oxide and oxygen
27. H.F. 56 F	Exploratory laparotomy and bowel resection 2–10–54	Meperidine 75 mgm. Atropine 0.4 mgm.	Thiopental-succinylcholine intubated ether-O_2	During operation	Ether overdose	Sigmoid resection 5–17–54 Excision rectal stump 8–5–55 Bladder suspension 9–19–56	Meperidine 50 mgm. Atropine 0.3 mgm. Meperidine 50 mgm. Scopolamine 0.4 mgm. Meperidine 50 mgm. Scopolamine 0.4 mgm.	Continuous spinal tetracaine dextrose Thiopental-ether-oxygen-curare intubated Thiopental-nitrous oxide-oxygen and ether
28. I.S. 64 F	Mastectomy cancelled 8–4–55	Morphine 8 mgm. Scopolamine 0.4 mgm.	Thiopental-nitrous-oxide, oxygen	During induction	Severe laryngospasm and anoxia	Excision breast tumor 8–16–55	Secobarbital 100 mgm. Scopolamine 0.4 mgm. and atropine 0.4 mgm. i.v. at operation	0.5% procaine local

The avoidance of arrest from hypoxia or asphyxia requires the establishment of a patent airway, adequate ventilation, the avoidance of substandard oxygenation in anesthetic mixtures, careful administration of muscle relaxants, and adequate removal of carbon dioxide.

The prevention of repeated cardiac arrest after hemorrhage, apart from sudden exsanguination, requires the establishment of a normal blood volume preoperatively and adequate hemostasis and blood replacement during the operative procedure. It is clearly the responsibility of the anesthesiologist to maintain adequate blood replacement during surgery in order to prevent shock and possible cardiac arrest. However, he has no control of those cases of sudden or excessively large exsanguination which must remain a surgical technical error.

The control of reflex cardiac arrest requires the recognition of the areas from which these reflexes occur, the prevention of hypoxia and hypercarbia which sensitize the heart to reflex stimulation, and the adequate blocking of these reflex arcs, either locally with procaine or by relatively large doses of intravenous atropine (0.5 to 1.0 mgm. or more). The carotid sinus in the neck and the cardiac center in the medulla are both sensitive to oxygen lack and hypercarbia. Sloan has shown that vagal inhibition of heart action is accentuated in the presence of hypoxia or hypercarbia.

The 1 case of myocardial infarction occurring in this series was recorded by the electrocardiogram preoperatively but was not recognized. The development of an unrecognized coronary occlusion some time in the preoperative period with subsequent cardiac arrest probably cannot be anticipated and will always remain a possible cause of cardiac arrest or death during operation. Occasionally patients die as a result of a

coronary occlusion just before coming to the operating room or in the anesthesia room prior to induction of anesthesia. If anesthesia were induced a few minutes earlier in some of these cases it would have been implicated improperly in the patient's death. There are also a few cases in which anesthesia and surgery have proceeded uneventfully and no gross errors have been made, yet the patient has a coronary occlusion and dies. This type of case cannot be attributed to anesthetic "cardiac arrest."

Although hypothermia has always been associated with a high incidence of cardiac conduction defects, the use of hyperventilation, antifibrillatory drugs, and injection of the sinoauricular node serves to reduce the severity of this complication. The incidence of cardiac complications is greatly increased during hypothermia when the surgery involves the cardiovascular system. A cardiac arrest in this group of patients must be considered "a calculated risk" as opposed to the sudden and unexpected cardiac arrest in the healthy patient undergoing corrective elective surgery.

Everyone who dies has a "cardiac arrest." Our major problem is the prevention of the sudden, unexpected complete cessation of cardiac action occurring in the operating room in the anesthetized patient.

3. The anesthetic agent or agents used or the method utilized have little bearing on the outcome of the case if properly administered. The dangers are those of overdosage or the improper use of an agent or method. In the cases in which cardiac arrest occurred there were 16 different anesthetic combinations used as contrasted to 17 different anesthetic combinations in the 42 subsequent operations. The only major reduction in usage of an anesthetic agent during general anesthesia in the subsequent operations was that of ether. At the time of cardiac arrest during general anesthesia ether was used in 18 of the 25 cases. In the subsequent operations ether was used at some time in 12 of the 29 general anesthesias. Cyclopropane, thiopental, and muscle relaxants were used in approximately the same percentage in both series of cases.

4. Preparation for surgery may be divided into two phases, the medical preparation and the preanesthetic medication. The medical preparation of the patient consists of bed rest, digitalization of the patient if in heart failure, and restoration of an adequate blood volume. In other words, the patient should be treated as though he had significant cardiac disease and disability before reoperation can be undertaken.

The problem of premedication has received considerable attention in the last few years, particularly from the laboratory of Reid, Stephenson, and Hinton. It is their belief that the administration of atropine at least every 1½ to 2 hours during operation will prevent cardiac arrest by blocking the vagus to prevent its effect upon the "specific tissue" of the heart. It must be remembered that complete blockage of the vagus in the human requires upward of 2 milligrams of atropine intravenously. The recommended doses of atropine given as premedication seldom cause an increase in pulse rate, when given intramuscularly, and produce only minimal vagal cardiac block. In this series, 7 of the patients who had cardiac arrest received atropine, 19 received scopolamine, and 2 patients received no premedication. Of the 7 patients who received atropine and had cardiac arrest, 5 received atropine for the next operation or operations. Two patients who had 1 subsequent operation received scopolamine for premedication and 1 patient who had 3 subsequent operations was given scopolamine premedication for the first 2 operations and atropine for the third. Of the 19 patients who received scopolamine before the arrest, 14 received scopolamine for the next operation or operations, and 5 received atropine. These 5 patients had operations performed with general anesthesia twice, local anesthesia twice, and 1 patient received no anesthesia. The patient who received no anesthesia had scopolamine for the first operation in which cardiac arrest occurred at the end of opera-

tion when a tight head and neck dressing was being applied after a radical neck dissection. The endotracheal tube was still in place and the patient's airway was not compromised by the dressing. It was believed at this time that this arrest was due to a hypersensitive carotid sinus. For the following operation, 6 months later, the patient received 0.5 milligram of atropine intramuscularly 45 minutes preoperatively and the operation was performed in the denervated area of the previous neck dissection. As a local tumor recurrence was being removed, this patient again exhibited a severe hypotensive episode in which the blood pressure and pulse were almost imperceptible. In anticipation of such a calamity an intravenous injection of 0.4 milligram of atropine (a total of 0.9 mgm.) was made and the blood pressure and pulse immediately returned to normotensive levels, even though total vagal blockade may not have been achieved. The problem of premedication has not been fully solved. Further reports of subsequent operations after cardiac resuscitation with the use of atropine and scopolamine as premedicant drugs should enable us to settle this vital problem yery soon.

5. In a series as small as this, it is not possible to state the probability of the occurrence of another cardiac arrest. The 1 patient in this series who died during the second operation, a partial hepatectomy, died from uncontrollable hemorrhage. The remaining 41 operations suggest that with adequate preparation and cautious anesthetic management, patients resuscitated from cardiac arrest can be reoperated upon successfully.

SUMMARY

A series of 42 subsequent operations after cardiac resuscitation is reported. There was only 1 death in this series due to exsanguination during a partial hepatectomy, which could not have been prevented despite all the safeguards suggested.

The preparation and treatment of these patients for reoperation in a manner similar to patients who have undergone varying degrees of myocardial ischemia after coronary occlusion have been discussed.

The anesthetic and surgical causes of the cardiac arrests are analyzed and methods of correction proposed.

This study indicates that no anesthetic agent need be avoided in operations performed after cardiac resuscitation if management is skillful.

The preparation of the patient for subsequent operations should follow that of any patient with previous myocardial ischemia presented for anesthesia and a surgical operation.

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AN EXPERIMENTAL AND CLINICAL EVALUATION OF SURGICAL SUTURE MATERIALS—III

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IN TWO PREVIOUS ARTICLES a theoretic basis for the choice of suture materials was worked out through experiments in animals and man. The histologic reactions around various sutures were examined, and at the same time their tensile strength in the tissues was determined.

The following conclusions were drawn from these investigations:

1. Untreated ("plain") absorbable suture materials display a marked exudative tissue reaction with a wide reaction zone and a delayed formation of collagen. This reaction influences the tensile strength of the wound which is already considerably weakened during the first 10 days after operation. Besides, the tensile strength of the thread is rapidly diminished because of the absorption of the suture, and, furthermore, the knots tend to slip however carefully they have been tied.

These suture materials are therefore considered unreliable for closure of fascial wounds, as disruption and incisional hernias must be expected. Neither are they safe for ligatures or for closure of the subcutaneous layers, as slipping of the knots may cause hemorrhage and wound hematomas or broad and ugly scars, and the marked exudation, where many sutures are inserted, produces seromas and increased risk of infection. Moreover, a remarkable amount of intraperitoneal adhesions are seen between the intestines and the peritoneal incision scar when plain absorbable materials have been used for closure of the peritoneum. These findings may account for some of the complaints of pain at the abdominal scar which are quite frequently encountered in patients even several months after operation.

2. The finer, nonabsorbable suture materials show very favorable tissue reactions as there is only slight exudation during the whole wound healing period, a rapid formation of collagen, and a rather small reaction zone. Accordingly, the strength of the tissue is not much impaired, the thread retains its initial tensile strength (minus 25 per cent reduction for some materials when wet), and the knots can be considered practically safe (except for monofilament synthetic fibers). They are less likely to produce intraperitoneal adhesions. Nonabsorbable suture materials, therefore, seem to be generally preferable for closure and ligatures in noncontaminated wounds. It must, however, be emphasized that gentle handling of the tissue and the use of the finest sizes are necessary to obtain a perfect healing result. There is no absolute agreement as to the advisability of using nonabsorbable materials also in contaminated and infected wounds. Some authors recommend fine silk or cotton even for that purpose, whereas others find that the risk of suture extrusion and persistent sinuses is too great. It has not been possible for me to form any opinion about this special problem through experiments in animals, as neither rats nor rabbits and pigs displayed any suture extrusions even when bad suture materials of very coarse sizes were inserted.

3. Tanned absorbable suture materials represent a compromise. Through treatment with chromic acid, tannin, iodine, or other chemicals their fiber structure is altered so that during the first days after insertion in the tissues they behave almost like nonabsorbable materials, with a moderate exudative reaction around the suture, a prolonged

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holding power of the thread, and a greater stability of the knot. Subsequent to the disappearance of the tanning chemical a retarded absorption with marked exudation takes place.

Tanned absorbable suture materials, if properly prepared, would seem ideal for buried sutures as no foreign body is permanently left. Knot extrusions are not very usual, and the threads can be relied on for ligation. The tissue reactions which they produce are, however, more marked than those around nonabsorbable materials, and they tend to cause quite extensive intraperitoneal adhesions. Besides, the manufacture of a homogenous thread of these materials with constant qualities is a quite difficult problem.

To make a clinical evaluation of these three different groups of surgical suture materials it is necessary to know the essential details about wound healing under normal and pathologic conditions. A thorough knowledge of the manufacture, preparation, and sterilization of the suture materials is equally important. Furthermore, facilities must be provided for a proper recording of the cases to be analyzed; every possible detail should be taken into consideration, not only what suture materials were inserted in the various layers, but also the history and clinical condition of each patient, the operation performed, the surgical conditions, and the postoperative period. Finally, a critical analysis of the results of a follow-up examination should be made by a surgeon thoroughly familiar with operative technique, and absolutely unbiased in his judgment. Such a detailed study must, of course, limit the number of cases available for statistical evaluation, but on the other hand, it is thought to be more informative than an estimation would be which was based upon a questionnaire sent out to a great number of surgeons who are asked to give their impression of the merits of the suture materials in question.

Concerning normal wound healing and the action of foreign bodies in normal tissues, the author refers to the many outstanding works of other writers. An elementary knowledge of fiber structures and their x-ray diffraction patterns will help to explain why various suture materials behave so differently in tissues. To illustrate the importance of a thorough information about the manufacture of the suture materials, iodine-catgut will serve as an example. Firstly, sterilization of catgut with iodine is not generally recognized as an effective method. Secondly, although many European manufacturers and surgeons call iodine-catgut a "plain" catgut, as distinct from "chromicized iodine-catgut," the former catgut is by no means plain. True plain catgut is sterilized by heat and has not been treated by chemicals at all. Iodine has a tanning effect similar to chromic acid and alters the fiber structure of the catgut so that absorption time is prolonged and knot stability is improved, but on the other hand the tissue reactions as a rule become more exudative during a longer period of days. It is also known that some products of American "plain" catgut have been slightly treated with chemicals before the thread is polished to make it uniform. This is, therefore, basically no true plain catgut, and this factor may well account for some of the discrepancies between the results of histologic and clinical studies obtained by various authors.

A vast literature exists on wound disruption, and many factors have been considered responsible for this dramatic type of wound complication. It seems reasonable to presume that incisional hernias are of similar origin, the only difference being that the skin and the superficial layers have not given way. But, as mentioned in part I, the trivial wound complications—hematoma, seroma, infection, delayed healing, ugly scars, and intraperitoneal adhesions—may occasionally have the same etiology as wound disruptions. On the other hand, extrusion of sutures, persistent sinuses, and stitch abscesses cannot always be attributed to the suture material chosen or the suture technique in itself.

The factors which have been taken into consideration as being theoretically of influence in wound healing complications can be grouped as follows: (1) factors concerning the preoperative condition of the patient—sex, age, race, nutrition, disposition for diseases, allergy, focal infections, previous operations, general condition, body temperature, fluid and electrolyte balance, and protein and vitamin intake; (2) factors concerning the operative technique in an extensive sense—operating room equipment, air sterility, skin disinfection, gloves and glove powder, instruments, dressing of the operating field, masking of the personnel, qualifications of the operator and assistants, duration of the operation, the trauma of the tissues, thoroughness of hemostasis, adequate blood replacement, placing of the incision, length of the wound, anesthesia, use of electrosurgery, drainage, dressing of the wound, and, finally, the suture materials chosen and the technique of wound closure and ligature; (3) factors concerning the postoperative period—fluid and electrolyte balance, protein and vitamin balance, body temperature, antibiotics and chemotherapy, anticoagulants, cortisone steroids, increased intra-abdominal pressure due to vomiting, coughing, ileus and aspiration, early mobilization of the patient, local treatment of the wound, and the number of days elapsing before removal of skin sutures or clips.

From personal experience and from the study of the literature it has been obvious that some of these factors, for instance sex and race, were of no demonstrable significance, and the importance of many other factors was very doubtful. For practical purposes the following factors were recorded for investigation, in addition to exact personal data to be used for the follow-up examination: (1) age; (2) disposition for diseases, and previous illnesses and operations; (3) height and weight; (4) laboratory findings; (5) clinical diagnosis; (6) type of operation and date of operation; (7) incision; (8) anesthesia; (9) operator, assistants, and operating nurse; (10) bacteriologic and histologic findings during or after operation; (11) suture materials used, and technique of closure in peritoneum, muscle, fascia, subcutaneous layer, skin and in other tissues, and the sizes used in the various layers and for heavy and fine ligatures; and (12) factors during or after operation which might influence wound healing. In each record was registered the primary wound healing result (on the last day in hospital, usually 10 to 14 days after the operation), and the secondary wound healing result (6 to 12 months after the operation).

CLINICAL MATERIAL

When this part of the investigation was started in 1949, nonabsorbable suture materials were very little used by the majority of the Danish surgeons, except for skin closure where silk and silkworm gut were preferred, with or without metal clips. For the deep layers and for ligation, catgut was generally used. The products traditionally chosen were iodine-catgut and peroxide-catgut of European manufacture.

For 1,211 patients under investigation the following three basically different types of suture material were selected: (1) plain (heat-sterilized, untreated) catgut manufactured by a Danish firm in close co-operation with the Copenhagen University Institute of General Pathology; (2) chromicized catgut (with a chromium content which secured the function of the suture for about 8 to 12 days when tested in rabbit fascia) provided by the same Danish firm; (3) a nonabsorbable suture material made of braided perlon, treated with wax and resins (unfortunately more exact information could not be given regarding this material, and its manufacture could not be controlled by the Institute) sold by a German firm.

Group 1 consisted of 471 patients in whom suture was with plain catgut by the following methods: continuous No. 2 sutures in the peritoneum, interrupted No. 2

in the muscle and fascia, no sutures in the subcutaneous fat, No. 0 sutures for ligatures, and silk stitches and Michel clips in the skin.

Group 2 was comprised of 280 patients in whom suture was with chromicized catgut by the following technique: continuous No. 0 stitches in the peritoneum, interrupted No. 1 in the muscle and fascia, no sutures in the subcutaneous fat, No. 000 for ligatures, and perlon stitches and Michel clips in the skin.

Group 3 included 460 patients in whom suture was with braided perlon by the following methods: continuous or interrupted No. 000 stitches in the peritoneum, interrupted No. 00 in muscle, interrupted No. 00 or 0 in fascia, interrupted No. 000 in subcutaneous fat, No. 000 for ligatures, and interrupted No. 0 stitches in the skin. The patients were common nonselected surgical cases, mostly gastroenterologic, biliary tract, appendicitis, hernia, goiter, and gynecologic operations, and also some urologic operations. The operations were carried out by 18 surgeons in Department H (General Surgery) of the Copenhagen County Hospital during the period from 1949 to 1954. For each individual patient a special record was meticulously kept as has been previously described.

The aim of the investigation was to find out: whether it is justifiable and safe to use nonabsorbable suture materials for closure of the deep layers and ligatures; whether the results of the experiments in animals, described in Parts I and II, could be confirmed by practical surgery; and whether the suture materials and the suture technique play any role at all in the production of wound complications in the surgical patients.

The author is perfectly aware of the fact that a valid statistical computation is out of the question, even if the groups of patients were 10 times as large. The multitude of factors to be taken into consideration, already enumerated, makes that impossible. The fact that 18 different surgeons performed the operations may be criticized, as all of them certainly could not be equally skilled operators. On the other hand, instructions for operative technique, asepsis, and operating room management in Department H are very strict, and all the difficult operations were performed by 5 or 6 surgeons with excellent training. Above all, the average results obtained by the whole surgical team are of practical interest when a certain suture material or suture technique has been used as a routine.

The patients of group 1 were operated on during the period from 1949 to 1951, group 2 in 1951 to 1952, and group 3 in 1952 to 1954, but the operations, anesthesia, access to antibiotics and anticoagulants, knowledge of fluid and electrolyte balance, and similar factors have been nearly the same during these 5 years.

It must also be admitted that the 3 groups of patients were not absolutely identical as to the relative numbers of cases of appendicitis, hernias, and cholecystectomies, but only approximately so. It might have been of greater significance to concentrate upon one or two operations with a fairly constant operative technique, for instance inguinal hernia repair and cholecystectomy. But it would have taken a much longer time and no impression would have been gained of how the suture material or the suture technique worked in all-round general surgery. Furthermore, in the ideal experiment the role of the suture material and the suture technique should be investigated separately. This is, however, impossible in practical surgery, among other things because the sizes which are considered proper when catgut is used would be much too coarse when braided perlon is chosen.

With these reservations the results of wound healing after operations on 1,211 patients of all three groups are presented in Table I. All patients were observed during the 10 to 14 days of hospitalization after operation, and in 185 primary complications were found. Quite often, more than one type of complication occurred in the same patient, for example seroma with en-

TABLE I.—COMPARISON OF RESULTS OF WOUND HEALING IN POSTOPERATIVE PATIENTS IN THREE GROUPS

	Primary complications			*Secondary complications*		
	No. of patients in groups	*No.*	*Per cent*	*No. of patients in groups*	*No.*	*Per cent*
Plain catgut, group 1.....	471	107	22.8	404	158	36.6
Chromicized catgut, group 2..	280	46	16.4	247	79	32.0
Braided perlon, group 3.....	460	32	7.0	390	101	25.9
Totals.....	1211	185		1041	338	

suing infection. In such cases only what was considered the more important complication was tabulated, so that the total number and per cent of patients who had primary complications could be estimated.

After 6 to 12 months 1,041 patients were followed-up, and secondary complications were observed in 338. Also in these only the most important complication was set down for each patient even if more than one type had occurred. Hereby the total number and per cent of patients who had secondary complications could be stated.

This distinction between primary and secondary complications was made, firstly, because during the first 10 to 14 days after operation almost the only complications encountered are hematomas, seromas, infiltration, secretion, wound infection, stitch abscesses, and wound disruption. It might also be useful to emphasize that the surgeon cannot feel sure about his suture material or suture technique merely from his impression of the number of complications occurring while the patients are still hospitalized. An equally important series of secondary wound complications may appear, sometimes quite late, after the patients have been discharged from the hospital. These complications include suture granulomas, suture extrusion, persistent sinuses, incisional hernias and recurrent hernias, pain at the scar, adhesions found at reoperation, and ugly scars. In Denmark, many of the late complications are seen only by the general practitioner, and actually some surgeons claim that they never have any wound healing complications at all in their patients, and that there exists no problem concerning suture materials and suture technique. This seems, indeed, to be a very doubtful postulate.

Only a few of the patients with secondary complications had also displayed primary complications, and the majority of the latter did not develop into secondary complications. The total number and per cent of patients who had either primary or secondary complications, or both, was surprisingly high: in group 1 there were at least 218 out of 471 patients or 46.3 per cent; in group 2, 105 out of 280 patients or 37.5 per cent; and in group 3, 119 out of 460 patients or 25.9 per cent.

As a whole, it appears from these figures that it is not only justifiable and safe but even advantageous to use fine nonabsorbable sutures for closure of the deep layers of abdominal incisions. It must also be admitted that this large scale experiment in patients has supported the theories previously advanced on the basis of the results of the experiments in animals.

Whereas it would be very difficult to prove how many of these complications can justly be attributed to inferior suture materials and faulty suture technique, it may to some extent be possible to tell what types of complications can be expected with different suture materials.

In Table II are shown the total number of the various complications which occurred in patients in whom plain catgut, chromicized catgut, and braided perlon, respectively, were used. The following types of complications will be discussed: (a) exudative complications which comprise hematoma, seroma, infiltration, secretion, granuloma, and infection; (b) wound disruptions; (c) incisional hernias (including recurrent hernias); (d) stitch abscesses; (e) suture extrusion (including granulomas and persistent sinuses); (f) pain at the scar (which may be caused by adhesions); and (g) ugly scars.

In Table III the percentage of occurrence

TABLE II.—TOTAL NUMBERS OF VARIOUS COMPLICATIONS IN EACH GROUP

	Group 1—Plain catgut		Group 2—Chromicized catgut		Group 3—Braided perlon	
Complications	Primary in 471 patients	Secondary in 404 patients	Primary in 280 patients	Secondary in 247 patients	Primary in 460 patients	Secondary in 390 patients
Hematoma	38	0	5	1	6	1
Seroma	25	23	4	18	3	0
Infiltration	8	0	16	0	7	0
Secretion	1	1	0	0	3	8
Infection	12	5	3	0	4	2
Granuloma	0	5	0	3	0	1
Suture extrusion	0	12	0	12	0	40
Incisional hernia	0	11	0	6	0	4
Wound disruption	2	0	3	0	0	0
Abdominal pain at scar	0	76	0	27	0	37
Adhesions at reoperation	0	4	0	0	0	0
Stitch abscesses	21	0	6	0	9	0
Ugly scar	0	20	0	9	0	8
Totals	107	157	37	76	32	101

of these types of complications in the three different groups are shown.

a. It is seen that the exudative complications are about 3 times as many with plain catgut, and twice as many with chromicized catgut, as with fine braided perlon. This observation strongly implies that the type of suture material plays a role, although it must be admitted that the finer sizes also may be of importance. The exudative complications mostly occur early after the operation, but may continue after the patients have been discharged from the hospital, or make their appearance later. They often prolong the hospitalization period and constitute a danger of infection which may be increasingly serious at present, with the virulent resistant staphylococcus strains now abounding in our hospitals.

b. The number of disruptions, fortunately, has been very small in these groups, actually too small to allow any definite conclusions to be made. It would be expected that disruptions occurred more frequently with the use of catgut than with a nonabsorbable material. On the other hand, it has been a surprise to find more cases of wound disruption in group 2 (chromicized catgut) than in group 1 (plain catgut). Other factors than the suture material may have been responsible, and it is a well known fact that even when nonabsorbable materials are used for closure of abdominal wounds, wound dehiscence is sometimes encountered. This occurrence is practically always in cases of increased intra-abdominal pressure. The suture does not break, and the knots hold fast, but the fascial tissue gives way because of pressure necrosis. If increased intra-abdominal pressure cannot be effectively combatted it is recommended prophylactically to apply an abdominal binder for at least 2 weeks.

c. The number of incisional hernias and recurrent hernias was also small, but the superiority of braided perlon over catgut can hardly be disputed. As previously mentioned, there is no fundamental difference between wound disruption and incisional hernia. In both instances the fascia has given way, but as a rule the defect is recognized later in hernia because the skin and subcutaneous fat still hold. Actually, there are transitional stages between these two types of wound complication.

d. Stitch abscesses are to a large extent dependent on the suture material used for skin closure. In the present groups of patients there were more than twice as many stitch abscesses when ordinary untreated silk was applied than when noncapillary braided perlon had been chosen. The abdominal skin can very seldom be kept sterile for more than a few hours at best, and as silk and other capillary materials are rapidly imbibed with serum they present a definite risk of infection. To illustrate this assertion further, the author analyzed a group of 385

TABLE III.—OCCURRENCE OF THE VARIOUS TYPES OF WOUND HEALING COMPLICATIONS IN THE THREE DIFFERENT GROUPS

Complications	*Group 1— Plain catgut, per cent*	*Group 2— Chromicized catgut, per cent*	*Group 3— Braided perlon, per cent*
Exudative complications (primary)	17.8	10.0	5.0
Exudative complications (secondary)	7.2	7.7	2.8
Wound disruption	0.4	1.1	0
Incisional hernia	2.7	2.4	1.0
Stitch abscesses	4.5	2.1	2.0
Suture extrusion	4.2	6.1	10.5
Cicatricial pain	19.8	10.9	9.5
Ugly scar	5.0	3.6	2.1

patients with superficial casualty wounds treated in the Surgical Policlinic of the Bispebjerg Hospital in Copenhagen. All the wounds were potentially contaminated, and only primary skin closure was performed. Of 214 patients in whom untreated silk had been used, 70 (32.7 per cent) had wound complications (stitch abscesses or wound infection). Of 131 patients in whom monofilament nylon was used, only 7 (5.3 per cent) had complications. Michel clips when used as the only material for skin closure in casualty patients showed very unfavorable results (12 complications in 40 cases, i.e., 30 per cent). Admittedly, other factors may have been of influence but the wound healing results in these 3 patient groups are so strikingly different that the role of the suture materials and the technique of closure cannot be missed.

e. Suture extrusion and its precursors, suture granulomas and persistent suture sinuses, are very annoying complications although seldom dangerous. Many surgeons attach so much importance especially to these complications that they are inclined to abandon any new suture material if extrusions occur, although these might stop completely provided the finer suture material only were used. Furthermore, patients are very much impressed by suture extrusions. The appearance of their wound is sometimes the only criterion by which they form their opinion as to the qualifications of the surgeon, and quite often they are frightened if sutures start protruding from the abdomen. Actually, it does not usually affect the wound healing result very much. As soon as a sinus appears in the scar, the surgeon should try to remove the underlying suture with a pair of tweezers. As a rule it can be done without anesthesia or under local anesthesia, and only occasionally is a thorough débridement necessary.

It is quite evident in the present analysis that nonabsorbable suture materials are more frequently associated with suture extrusion than catgut, in fact twice as often as plain catgut. However, this is the only point in which nonabsorbable sutures were inferior to catgut, and it should impel the surgeon, not to abandon nonabsorbable suture materials, but to make every possible effort to minimize the occurrence of suture extrusions by improving his technique of gentle handling and by choosing the finest sizes of the most suitable nonabsorbable material.

f. Some surgeons flatly deny that suture materials play any role in the production of cicatricial pain. On the other hand, a painful ileus is quite often caused by intraperitoneal adhesions after a previous operation. It has been proved experimentally in animals that adhesions between the intestines and the peritoneal wall were more abundant when catgut was used for closure of the peritoneal incision than when nonabsorbable materials had been inserted. Therefore, it does not seem a very farfetched assertion that the suture material may account for the much greater number of complaints of pain encountered in the plain catgut group (19.8 per cent) as compared with the braided perlon group (9.5 per cent). In both groups of patients the same incisions were used and the same glove powder (absorbable starch powder).

g. All the problems concerning ugly scars have not yet been solved. In many cases it seems probable that both the suture material used and the technique of closure may be of consequence. Some surgeons never close the subcutaneous layer with sutures, and use

metal clips for the skin incision. If the latter are removed after 6 days as a routine, as is very often done in Danish hospitals, there may be a considerable risk of broad scars later, especially after abdominal operations. If plain catgut sutures are used in the subcutaneous layer, one will have to expect an increased amount of exudation around each suture, a tendency of the knots to slip, and absorption of the thread after only a few days, so that the holding power of the sutures is quite illusory.

The number of cases of ugly scars has actually decreased in the group of patients in which thin braided perlon sutures were used both for the subcutaneous layer and for the skin, as compared with the plain catgut group in which the subcutaneous layer was not sutured at all (2½ per cent against 5.0 per cent).

CONCLUSIONS

The results of wound healing in 3 fairly comparable groups of patients indicate that the number of wound complications can be reduced by general use of fine nonabsorbable suture materials instead of catgut for closure of clean abdominal wounds and for ligatures, as would be expected from the results of experiments in animals. All types of wound complications, except suture extrusion, were fewer with nonabsorbable suture materials.

As long as better suture materials are not available the surgeon will have to choose between, on the one hand, a considerable number of exudative complications with eventual wound infection, an increased risk of wound disruption, incisional hernias and recurrent hernias, a greater incidence of ugly operation scars, and possibly a greater number of patients with postoperative cicatricial pain, but not many suture extrusions, as characteristic of catgut, and, on the other hand, generally satisfactory wound healing, but occasional suture extrusions, as seen with most of the nonabsorbable suture materials.

In the present article, only the three different basic groups of suture materials have been dealt with. In recent investigations carried out in other hospitals upon large groups of patients deep layers were sutured with silk, linen, and dacron, respectively; and results similar to the perlon group were obtained. These results are to be published later, and at the same time an opinion will be given about what suture material and what suture technique are considered to be preferable for general and special surgical use.

As a preliminary, it can be ascertained that as yet no ideal suture material exists for universal purposes. The use of plain catgut should be very limited as it is unreliable. Tanned catgut should, for the present exigency, be reserved for contaminated or infected wounds and for a few special purposes, particularly sutures in the proximity of the mucosa of the urinary and biliary tracts where the risk of calculus formation is greater the longer a foreign body remains.

For deep sutures in clean wounds fine nonabsorbable sutures are of advantage, preferably as interrupted sutures, and for skin closure fine noncapillary suture materials should always be used. The skin sutures as a rule should not be removed too early, after 14 days rather than after 10 days, with the exception of cosmetic facial and cervical sutures. Metal clips might actually be abandoned. Some of the new synthetic fibers, especially the polyesters dacron and terylene, have showed very promising results in practical surgery. They are less elastic than nylon, and they are suitable for ligatures as well as for closure of the deep layers and the skin. Their low capillarity is possibly the reason why they are less likely to become extruded than, for instance, untreated linen and silk. Furthermore, as their tensile strength is great and quite constant, provided they have been adequately sterilized by autoclaving and not resterilized, they can be safely used in very fine sizes, and the foreign bodies inserted are therefore small. Possible they will supersede catgut as the suture material of choice, as it appears

that better results in wound healing can be obtained at a lower cost when these materials are used.

Whether catgut or other absorbable materials may be further improved so that they can reclaim their previous superiority remains to be seen. Competition within this field will be welcomed by surgeons who are interested in uncomplicated wound healing.

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NUTS, EGGS, AND CANCER

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ASSOCIATION of the above items is indeed obscure. They are completely unrelated except as used by the medical profession to describe sizes and shapes of various tumors. Comparing man's lumps and growths to edibles of one kind or another is a more or less universal trait of doctors. Like it or not we have inherited this form of description from our medical ancestors. Unfortunately we will pass it on to posterity with continued inaccuracy but with much enthusiastic local color.

While making a follow-up study on carcinomas at two of our local hospitals the writer was struck by the odd assortment of articles used to describe the size of a particular tumor. As the study proceeded the descriptions on the hospital charts seemed to grow more fantastic. Therefore, a list was made of some of the more vivid comparisons.

From a medical standpoint we can take no pride in the resulting compilation. True, it is colorful, but there any virtue ends. The descriptions may have been accurate for size to those who wrote them on the chart, but to reviewers at a later date, the result is very different.

There seems no limit to which the various types of eggs, fruit, or nuts may be compared to the physical properties of a tumor. In fact, often the chronicler must have been hard pressed to finally come forth with "small pullet's egg" or "stuffed olive." It is difficult to understand the popularity of this descriptive form against the English or metric system of measure. As will be noted the gustatory influence is exceedingly strong. It far overshadows the no less imaginative comparisons with "balls, coins, or babies' heads." It is assumed that this represents a cross section of the describer's thoughts at the time of recording. If this is true—then it might well be said that the medical profession, like Napoleon's Army, travels on its stomach.

The following list indicates estimated tumor sizes as recorded in hospital charts of the Indianapolis General Hospital and the Indiana University Hospitals. They were not made by students, technicians, or nurses. They were made by doctors, both resident and attending.

Egg, small egg, duck egg, goose egg, guinea egg, hen's egg, large egg, robin's egg, pigeon egg, quail egg, small pullet's egg, banty egg.

Walnut, hazelnut, hickory nut, English walnut, hulled walnut, hull of walnut, pecan acorn, unhulled walnut, large pecan, half a hickory nut, chestnut, large peanut, almond.

Grain of corn, few grains of maize, bean, kidney bean, navy bean, pea, lentil seed, soup bean, split pea or grain of wheat, millet-sized.

Orange, small orange, lemon, small lemon, lime, grapefruit, small grapefruit, large grapefruit, half the size of a lemon, cherry, small plum, large orange, two large oranges, tangerine (large), half grape, melon, half a banana, dried prune, watermelon seed, peach.

Stuffed olive; cup cake—flat on top.

Dollar, dime, nickel, quarter, half a dollar, dollar and a half, dollar bill, mass the size of five quarters stacked on one another, a fifty-cent piece.

Baseball, third of a baseball, tennis ball, golf ball,

billiard ball, ping pong ball, football-sized mass, volley ball.

Fist, hand, thumb, tip of thumb, end of little finger, child's fist, as big as a man's head, baby's head, as big as two thumbs.

Saucer, dinner plate, tea cup, coffee cup.

Pencil point, pin head, eraser in a lead pencil, match-head, B-B shot.

Jaw swollen to size of a good case of mumps.

This method of describing tumor sizes is common practice in many institutions and is not merely a local situation. It is as popular among the older doctors as with the younger. The moral is obvious—a plea for accurate descriptions of tumors using the English or metric system rather than by inaccurate though more colorful comparisons. In expressing this wish it is fully realized that no change will be made and that we will continue to scramble eggs, nuts, and cancer.

THE INDIVIDUAL BASIS OF BIOLOGIC VARIABILITY IN CANCER

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ALMOST 10 YEARS AGO I suggested the phrase "biologic predeterminism" as a synoptic expression for a biologic balance between host and neoplasm, established before the neoplastic process becomes clinically detectable. Evidence in support of this concept, as presented originally in the pages of SURGERY, GYNECOLOGY AND OBSTETRICS,[1] supported an obvious corollary: the outcome of the preclinical struggle for power, between a developing neoplasm and the enigmatic defensive reactions of the host, is of greater prognostic importance than the time or type of treatment.

Biologic predeterminism either has been endorsed or rejected by exponents of two contrasting philosophies concerning the effectiveness of surgical therapy for cancer, but both seem to mistake predeterminism for a biologic equivalent of the doctrine of uniform predestination, or Calvinism, in theology. Some cynics have assumed that predeterminism is in agreement with those deft but dour wizards of biometry, Park and Lees, who suggest that the course of cancer of the breast is uninfluenced by treatment. On the other side of the philosophic fence protagonists of surgical superradicalism who represent "the triumph of hope over experience" employ such expressions as "a prophet of doom" in tirades decrying any recognition of the biologic facts of neoplastic life. The "new" radicalism so eloquently advocated on one such occasion, that of neck dissection complementary to radical mastectomy, seems to have been as futile an exercise in Minneapolis as it had been 50 years previously in Baltimore.

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[1]MACDONALD, I. Biological predeterminism in human cancer. Surg. Gyn. Obst., 1951, 92: 443.

Any thoughtful surgeon or radiotherapist of experience recognizes the circumscription of conventional techniques in cancer therapy. Our present inability to control cancer effectively in more than 30 of each 100 patients provokes a laudable discontent manifested by a wide variety of attitudes. Under utopian conditions salvage might approach 50 per cent, and this fact emphasizes the limited promises of more public information, more extensive operative procedures earlier in the symptomatic phase by competent surgeons, and broader distribution of radiologists who are capable of administering irradiation with skill and genuine therapeutic intent.

As these facts become inescapable, extremists of opposite philosophies labor to extend further their particular forms of immoderation. Cynicism *based on statistical formulas*, untempered by clinical knowledge, has arrived at the ultimate absurdity of ivory-towerism in concluding that treatment of any sort decreases longevity! Defeatism in surgical therapy is represented by those who fail to recognize the individual basis of biologic variability which determines the potential value of extirpative measures. The futility, or even the unfavorable effects of surgical treatment in some forms of cancer, should not obscure the curative and palliative accomplishments of adequate, meticulous, operative procedures for many patients. The proper surgical management of cancer is responsible for the major share of present rates of clinical control, and while many of the procedures employed are far from ideal or even desirable, the prospect of their replacement by approaches of specific and less unphysiologic nature seems remote.

In contrast to the passive reactors and cynical nihilists are the extreme actionists, who believe that by extending present techniques to maximum levels much of the total problem can be solved. Representative of this philosophy are surgeons who employ "extended" operations for biologically incurable disease, and radiotherapists so entranced with super-high sources of energy, or isotopic substitutes, that they seem to forget the critical factor of radiosensitivity of neoplasms. More often than not, extremism is benefited by well meant efforts of educators in their continuous, unmerited emphasis of the timeworn opiate of "early diagnosis, prompt treatment."

Those who regard predeterminism as an expression of therapeutic futility must reject entirely the inexorability of natural selection in cancer. Some types of cancer do have a natural history which generally conforms to the traditional doctrine that curability is directly related to the "earliness" of diagnosis, the "immediacy" and effectiveness of treatment. These are forms of cancer in which both the degree of space occupation by the primary neoplasm, and the anatomic extent of regional and distant metastasis, is a function of chronologic duration. Such is the natural history of squamous carcinomas of the skin, lip, and uterine cervix, which represent a mid-zone in the spectrum of biologic predeterminism.

At one extreme of this neoplastic spectrum are indolent lesions, the malignant potential of which may not become apparent for many years, and in which the histologic structure often is misleading. "Benign" mixed salivary gland tumors, metastasizing thyroid lesions of orderly histology, and certain fibroblastic neoplasms are typical examples. The extreme "high energy bands" are represented by cancers which usually originate as diffuse multifocal neoplasms—the lymphoblastomas, leukemias, and myelomas. Almost as ominous are some primary carcinomas which may disseminate widely soon after the phase of invasiveness is achieved; examples all too familiar clinically are melanoma, a majority of mammary, gastric, and bronchogenic carcinomas, and some connective tissue sarcomas.

Yet, all of these ordinarily lethal forms of cancer include some fraction in which the struggle between host and neoplasm has eventuated in confinement of the invader to an anatomic beachhead, from which it may be dislodged permanently by a single, sweeping *tour de force*. In some instances the job is done best by a surgical team; in others a radiologic detail operating conventional equipment intelligently will have the same curative effect as the jet-electronic cannons and barbecues currently so favored by headline writers and fund-granting agencies. In still other patients the antineoplastic campaign of choice is a combined action of cooperating surgical-radiologic task forces, a joint attack achieved with efficient anonymity to an increasing extent.

Predeterminism emphasizes one feature of cancer therapy overlooked by those whose traditional concepts of space, time, and earliness neglect the fact that chronologically "late" cancer also may be curable. Predeterminism indicates grouping by natural selection in specific neoplasms, and mammary carcinoma is an excellent example. For each 100 patients, about 20 will present dilatory lesions still limited to the breast 3 or more years after onset; some 55 will have developed distant dissemination in the occult or preclinical phase; in 25 there is a sequential time-space relationship, and for these women prompt diagnosis and treatment may be lifesaving. As yet, we have only inexact criteria for the separation of individual patients into one of these biologic groups. But we can muster enough total evidence from various sources (history, physical signs, radiography, histology, biopsy of scalene or contralateral axillary nodes) to eliminate most of the harm inflicted by "early" or, still worse, "immediate" treatment. "Immediate" treatment is translated too often into an "emergency" both by patient and surgeon, and unfortunately the evangelistic educators make the removal of a suspect

lump sound as emergent as the operative treatment for acute appendicitis.

It is desirable to use sedation before the scalpel to avoid useless mastectomies, and, of equal importance, to avoid failure to perform mastectomy in some "late" cases. The emphasis on "early" treatment condemns to palliative treatment all women with signs of local extension which are traditional stigmas of incurability. Bulky primary mammary cancers, ulceration, or even pectoral fixation are not per se criteria of inoperability. If clinical evidence of regional (axillary) spread is unimpressive, curability in such patients may be a function of delay, or "lateness." Each clinical situation is an individual therapeutic problem, as so eloquently emphasized by George Crile, Jr., in recent years. Unlike Crile, we retain our belief in conventional radical mastectomy as the most useful definitive procedure, but the favorable modification of natural history by treatment in Edinburgh and San Francisco, in Cleveland, and upstate New York, is more a reflection of predeterminism than of variations in therapeutic methods.

Adherents of the traditional concept of "earliness" suffer their rudest reversal when confronted with evidence of a negative association between delay and "curability." Blalock and Ochsner recently noted that every malignant lesion (*sic*) is a "law unto itself," that "subtotal gastrectomy . . . results in a rate of cure equally as high *if not higher*" than total gastrectomy, and reported an average duration of symptoms of 11.3 months for 5 year survivors and 7.6 months for nonsurvivors. Having made these concessions to the unpalatable truths of biologic life in gastric carcinoma, symptoms of intellectual dyspepsia led to a remarkable denial of the significance of their own data, as follows: "The fact that long-time survivors usually have had longer durations of symptoms in no way supports the contention of Macdonald and Kotin" concerning the fallacy of early diagnosis in this disease. The largest series of gastric cancer with follow-up in world literature (Waltman Walters and associates), as well as smaller samples accurately studied, demonstrate an inverse relationship between delay, and both resectability and survival, in gastric carcinoma.

In the face of these established facts, "educational" inundation of the medical profession with outworn slogans and intellectual placebos continues unabated. Monographs on cancer of the stomach and lung keynoted as "problems in early diagnosis" were excusable even 10 years ago; today they are typical of the continuing refusal of many teachers in surgery to abandon a traditional, uniform approach to all forms of cancer. Gastric and pulmonary cancers present such extremely limited curative possibilities by surgical treatment that even under the most ideal conditions less than 10 per cent of patients achieve long-term survival. It is inconceivable that earlier discovery of carcinoma of the breast could produce an increase in 5 year survivals of more than twofold, as estimated in some items of professional propaganda. The limited usefulness of conventional methods is as distressing to converts to predeterminism as to the skeptics, but the educational sedation provided by a failure to recognize such limitations prevents a wider understanding of the total problem.

Such neoplasms are not problems in early diagnosis, but problems awaiting the development of totally new methods of treatment, yet to be born of research. In the meantime, the surgeon's responsibility is the recognition of cancer at a biologically early phase, which may or may not be compatible with earliness in the temporal or dimensional sense. Each patient is an individual problem; the attack on a specific neoplasm should be conditioned upon a knowledge of its usual biologic pattern and the best evaluation possible of its behavior in the individual.

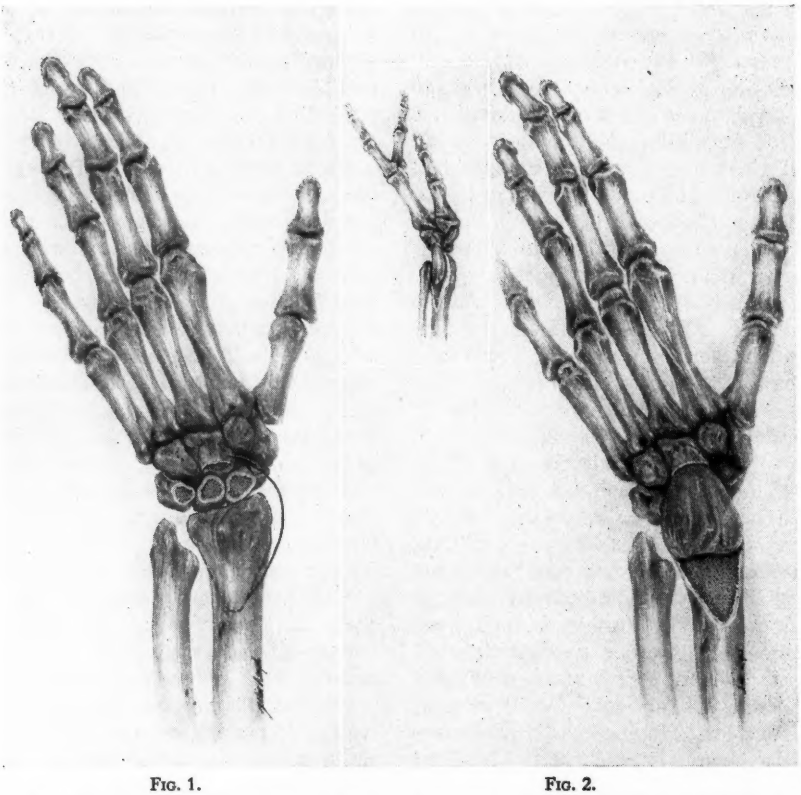

FIG. 1. FIG. 2.

FIG. 1. This drawing shows the outline of the turnabout bone graft from the distal radius. Denudation of the proximal carpal row and construction of the cleft in the capitate have been carried out.

FIG. 2. Dorsal surface of wrist and hand is shown with turnabout radial graft removed and in position. This graft crosses the denuded carpus, and its distal end is buried in the cleft cut in the capitate. The inset shows locking of radial graft in the functional position of wrist dorsiflexion.

Gill Turnabout Radial Graft for Wrist Arthrodesis.—Irvin Stein.

THE SURGEON AT WORK

GILL TURNABOUT RADIAL GRAFT FOR WRIST ARTHRODESIS

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In 1923, A. Bruce Gill devised a most ingenious method for wrist arthrodesis. He reasoned that an arthrodesis required bone structurally strong with large contacting trabecular surfaces that favored early incorporation of the graft. In other words, the combination of stability with active osteogenetic potential is of paramount importance.

Within this period, Steindler had published a report upon wedge resection in 1918. Eby, in 1920, had reported on the use of a tibial graft. In 1942, Abbott reported that for over 20 years he had used a method employing cancellous iliac bone strips.

It is interesting that Gill independently appreciated the value of cancellous bone but, nevertheless, realized that the ideal method still embodied the use of both cancellus-like structure for osteogenesis and compact or cortical bone for stability. To this procedure he added the original concept of the turnabout graft from the lower end of the radius. Thus, no additional operative procedure was required for donor material. Furthermore, the shape of the lower end of the radius when turned 180 degrees on the coronal axis is such that it fits well into the arthrodesis bed while maintaining the optional extension (dorsiflexion) position of the wrist.

TECHNIQUE OF OPERATION AS DESCRIBED BY GILL

The wrist is exposed through a longitudinal dorsal incision which is centered over Lister's tubercle and is adequate to expose the lower 2 to 3 inches of the radius and to reach the bases of the metacarpals. Appropriate denudation of radial and carpal surfaces is carried out. Any fibrous or granulation tissue which is present is excised.

SUMMARY OF CASES OF ARTHRODESIS OF WRIST

No.		*Diagnosis*	*Date*	*Operative procedures*
1.	H.M.	Poliomyelitis	6-12-23	Arthrodesis shoulder and wrist
2.	R.H.	Poliomyelitis right upper extremity	3-23-28	Arthrodesis right wrist combined with arthrodesis carpo-metacarpal joint right thumb
3.	L.M.	Left spastic hemiplegia	11- 5-28	Arthrodesis left wrist. Transplantation of flexor of wrist to extensor of fingers and thumb
4.	E.U.	Right spastic hemiplegia	11-18-29	Right wrist arthrodesis
5.	V.K.	Spastic paralysis right	12- 2-29	Right wrist arthrodesis
6.	V.R.	Right spastic hemiplegia	12- 2-29	Arthrodesis right wrist. Tenotomy of flexors right little finger
7.	W.P.	Ankylosis of wrist	3-13-30	Arthrodesis left wrist
8.	J.I.	Right spastic paralysis	11- 7-30	Right wrist arthrodesis
9.	P.C.	Brachial palsy	4- 3-31	Tendon transplant. Wrist arthrodesis
10.	P.S.	Dislocated lunate left	6- 6-33	Arthrodesis left wrist
11.	V.W.	Poliomyelitis left arm and shoulder	1-25-37	Tendon transplants arthrodesis left wrist
12.	W.D.	Old scaphoid fracture right wrist	3- 2-38	Right wrist arthrodesis
13.	M.H.	Brachial birth palsy	4-17-39	Arthrodesis right wrist
14.	C.E.	Poliomyelitis right upper extremity	5- 8-39	Arthrodesis right wrist
15.	L.B.	Right spastic hemiplegia	10-15-46	Arthrodesis right wrist. Transplantation flexor carpi ulnaris to flexors of thumb and index finger

FIG. 3. L.B. Case 15. Three months after operation following removal of plaster. The outline of the radial graft extending from the radius into the capitate is observed on both anteroposterior and lateral views.

FIG. 4. L.B. Case 15. Roentgenogram which was taken 3 years after operation was performed. The radial turnabout graft has been completely incorporated into both areas. Wrist fusion is firm.

A cleft is made in the os magnum (capitate) transversely in the coronal plane. A broad plate of bone is then removed from the lower posterior aspect of the radius. This plate of radial bone is then rotated or turned about 180 degrees in the coronal plane. The sharp proximal end of the radial graft is driven into this cleft in the os magnum (capitate). The cancellous surface of the graft is, of course, maintained in contact with the cancellous surface of the denuded carpal and lower radial fusion bed (Figs. 1 and 2). Upon slight dorsiflexion of the wrist the bone plate locks into the os magnum (capitate) and firmly contacts the posterior surface of the radius as well (Fig. 2).

Ligaments are sutured over the graft and the wound is closed without drainage, and dressed in plaster. The plaster should extend from the axilla to the knuckles with the elbow bent at 90 degrees and should be cut back at the proximal palmar crease in order to assure freedom of finger motion.

SUMMARY

An original method for wrist arthrodesis devised by A. Bruce Gill is presented. It was first performed in 1923. This procedure consists of a turnabout graft taken from the distal radius and inserted into a transverse cleft in the capitate.

This graft affords the stability of cortical bone combined with wide apposition of cancellous or trabecular surfaces. It furthermore affords a shape that conforms to the desirable angle of dorsiflexion of the wrist after fusion.

The 15 cases presented are all Doctor Gill's to whom the author is indebted for his clear outline of the principles and operative procedure, and for the opportunity to present his cases.

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TREATMENT OF MALLET FINGER BY COMPLETE METACARPOPHALANGEAL FLEXION

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THE TREATMENT OF INJURY to the extensor mechanism of the distal phalanx at its insertion continues to present a difficult problem for the surgeon. The deformity referred to as mallet finger is a result of either an avulsion of the extensor slips of tendon or an avulsion chip fracture of the dorsal and proximal portion of the phalanx with the attached tendon. In many patients the deformity is of little consequence except from a cosmetic standpoint. In others, whose occupation or other activities require manual dexterity, the deformity presents an additional imposing functional problem.

There is considerable variance in the extent of treatment which is recommended by surgeons today. This is, undoubtedly, to some extent related to the skill and experience of the surgeon. Many skilled hand surgeons recommend immediate operative repair in all cases; others recommend conservative measures when treatment is instituted early. Some surgeons, inexperienced in hand surgery, believe that the results do not justify any treatment whatsoever.

HISTORICAL DATA

Although it is fully appreciated that any incident of rapid flexion of the distal phalanx without relaxation of the extensor mechanism may produce this deformity, the frequency of occurrence with catching a thrown object on the tip of the finger has resulted in the term, "baseball finger." It is probable that the mallet finger deformity dates back to the era when man first began throwing objects either to or at one another. In 1930, when the treatment in vogue was the application of the straight splint with hyperextension of the distal phalanx, Mason recommended operative repair as the treatment of choice because of the unacceptability of the results of the closed method. He called attention to the tendency of the tendon to heal in the lengthened condition, and also believed the distal interphalangeal joint capsule to be torn in all cases. Platt, in 1931, first suggested minimal flexion of the proximal interphalangeal joint for the purpose of preventing subluxation with hyperextension of the joint. In 1937, Smillie called attention to the relaxation of the extensor slips to the distal phalanx obtained by proximal interphalangeal joint flexion. He advocated and demonstrated an excellent technique for tubular cast application in this position. Bunnell subsequently explained the advantage of proximal interphalangeal flexion by demonstrating the volar shift of the lateral slips of the extensor expansion with a gain of approximately 3 millimeters in length. In addition, the accepted excellence of the pull-out wire technique of tendon repair, plus the advent of antibiotics gave new impetus to those who believed in the value of operative repair.

ANATOMIC CONSIDERATIONS

The extensor expansions of the fingers are an aponeurotic continuation of the tendons of the extensor communis. By virtue of its insertion into the bases of the proximal phalanges, extensor communis action is mostly spent with extension of the metacarpophalangeal joint. Extension of the interphalangeal joints is a manifestation of the function of varying combinations of the intrinsic muscles of the hand. The dorsal interossei all possess an insertion into the bone of the proximal phalanx to permit the action of deviation from the middle finger. This insertion could have no role in producing extension of the interphalangeal joints. In the second, third, and fourth dorsal interossei there is an additional insertion into the extensor expansion which plays a supplementary role in producing extension of the interphalangeal joints. It is noteworthy that these insertions arise from separate muscle bellies which are ventrally positioned in the dorsal interosseous muscle. The extent of the secondary insertion is increased in those dorsal interossei

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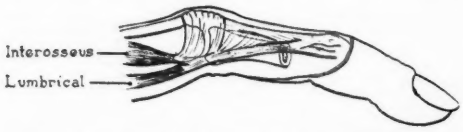

FIG. 1. Extension of distal interphalangeal depends on intrinsic hand muscles. Immobilization of musculotendinous expanse must include flexed metacarpophalangeal joint.

which insert on the ulnar side of the finger where no lumbricalis is present.

The volar interossei with rare exception are inserted wholly into the extensor expansion and in addition to their adducting and metacarpophalangeal flexing function, they play a major role in supporting the interphalangeal extending function of the lumbricales. The lumbricales arising from the flexor profundus tendons course volarward to the interossei and the deep transverse ligaments of the palm, and are inserted into extensor expansion at a point distal and lateral to the interossei. The abductor digiti quinti arising from the pisiform and inserting into the extensor expansion assumes the role of an interosseus on the ulnar aspect of the little finger.

By virtue of the volar relationship of the origin to the insertion of those intrinsic muscles which function to produce interphalangeal extension, metacarpophalangeal flexion is an inherent additional function of all.

DISCUSSION

Irrespective of the presence or absence of a bone fragment, the pathologic condition is essentially the same. There is disruption of the continuity of the musculotendinous mechanism. The immobilization most popularly employed today is phalangeal. Such immobilization is limited to only the tendinous expanse of the interphalangeal extensor mechanism and disregards the muscular expanse. A cardinal principle in the treatment of tendon injuries, by either closed or open measures, is immobilization of the complete musculotendinous mechanism in the relaxed position. The relaxed position of any musculotendinous structure is the position which most closely approximates the site of origin and the insertion. Complete relaxation of the interphalangeal extensor mechanism can, therefore, not be obtained without metacarpophalangeal flexion. Failure to include this joint parallels treatment of flexor tendon injuries of the hand without inclusion of the wrist and elbow.

These observations become more apparent to the surgeon upon examination of his own hand. As illustrated in Figure 2, with metacarpophalangeal flexion and flexion of the proximal interphalangeal joint, extensor power in the distal phalanx is lost indicating tendon relaxation. As illustrated in Figure 3, with extension of the metacarpophalangeal joint, even though flexion is retained in the proximal interphalangeal joint, extensor power is retained in the distal joint. This is in definite contradiction to Smillie's belief that extension of the distal phalanx is impossible with flexion of the proximal interphalangeal joint. It is noteworthy that the extended position of the metacarpophalangeal joint is the one most frequently assumed by the patient with phalangeal immobilization to prevent the casted finger from interfering with the function in the rest of the hand during the period of immobilization.

It must be appreciated that when a bone fragment is present, a roentgenogram will reveal the distal shift of the tendon and approximation of the fragments. Under these circumstances a good result may be anticipated if the fracture is immobilized in the reduced position for a sufficient period of time to permit union to occur. In the absence of an avulsed fragment, there is no criteria to guarantee approximation between the tendon ending and the site of avulsion. In the fresh case, the presence of edema and a capsular tear may be responsible for preventing the necessary distal shift of the tendon ending. In those cases in which treatment is delayed for even a short period of time, the natural healing tendency of the tendon at the site to which it withdraws may prevent such a distal shift. It should, therefore, be appreciated that a certain percentage of cases are doomed to failure irrespective of the mode of treatment or of the interval between the injury and the initiation of treatment.

It is only natural that some concern may be manifest regarding the possibility of developing a flexion contracture of the metacarpophalangeal joint as a result of prolonged immobilization in the completely flexed position. The authors have never seen a flexion contracture of the metacarpophalangeal joint resulting from prolonged immobilization and have no knowledge of its occurrence. The high incidence of extension contractures at this site and the apparent infrequency or absence of flexion contractures are explainable on the basis of capsular anatomy

FIG. 2.

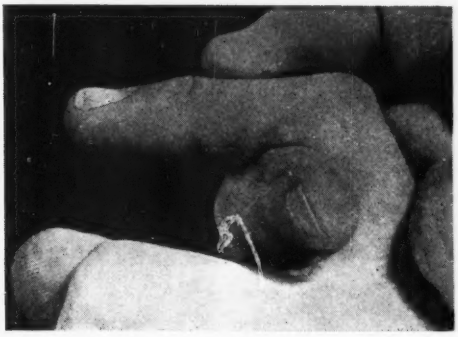

FIG. 3.

FIG. 2. With metacarpophalangeal flexion, no resistance can be offered to passive flexion of the distal interphalangeal joint indicating complete tendon relaxation.

FIG. 3. Although proximal interphalangeal flexion is retained, with hyperextension of the metacarpophalangeal joint active extension of the distal interphalangeal joint is still possible indicating incomplete relaxation.

(Fig. 4). In the extended position the capsular ligaments are relaxed to permit abduction and adduction of the finger and immobilization in this position may result in shortening of these ligaments and consequent extension contracture. In the flexed position, the capsular ligaments are taut and no shortening can occur.

SURGICAL TREATMENT

In this article our purpose is to stress the importance of adequate immobilization and to discuss the rational of the immobilization. We have no desire to recommend any specific method of surgical repair. In our series, the Bunnell pull-out wire technique was utilized in all cases. In each instance, the extensor tendon was shortened several millimeters which procedure is believed to have a twofold advantage. It freshens the end of the avulsed tendon and, in addition, removes any laxity from the extensor mechanism. Instead of inserting the wire through the end of the tendon as illustrated by Bunnell, it was brought out on top of the tendon (Fig. 5) to avoid the presence of the wire at the site of the healing and also to approximate the tendon better to the site of the avulsion. We could see no advantage to removing the suture at the end of 3 weeks, and in our cases the suture was permitted to remain throughout the entire 5 week period of immobilization. This procedure resulted in the additional advantage of eliminating a cast change. No complications were thus encountered. Before closure of the wound, the wire was tested to assure stability of the suture and to observe the approximation of the tendon end to the base of the phalanx. The tying of the wire suture was the last step of the operation and was done after the application of the cast. This procedure obviates the possibility of breaking the wire suture while applying the cast. It is appreciated that breaking the wire suture in tying it under tension could present a problem, but we have been fortunate enough not to encounter this mishap.

CAST APPLICATION

The cast application requires the maintenance of 3 pressure sites which should be sufficiently but not too well padded. Pressure is required on the dorsum of the proximal phalanx to maintain

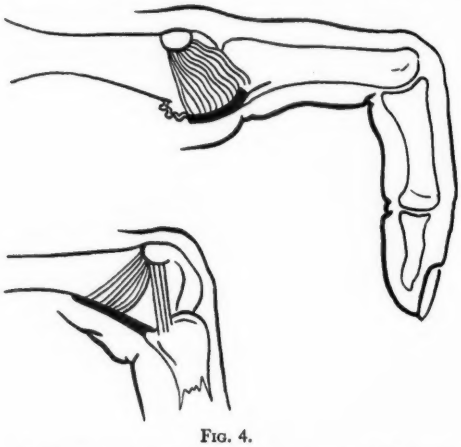

FIG. 4.

FIG. 4. Capsular ligaments of the metacarpophalangeal joint are relaxed in extension and taut in flexion. Contracture not probable when finger is in flexed taut position.

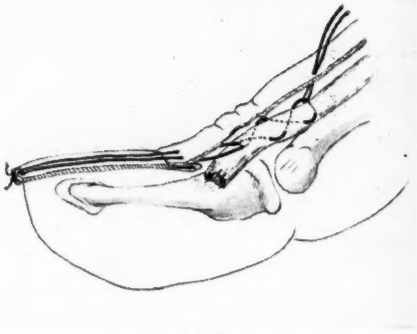

FIG. 5.

FIG. 5. Dorsal exitus of the end of the tendon suture forces the tendon end into approximation with the avulsion site. Additional silk sutures may be used for reinforcement.

flexion of the metacarpophalangeal joint, on the dorsum of the middle phalanx to maintain flexion at the proximal interphalangeal joint, the palmar surface of the distal phalanx to maintain hyperextension in the distal interphalangeal joint. Pressure is not required over the dorsum of the distal phalanx, and its absence there at the site of the avulsion contributes to the comfort of the patient. In addition, exposure of the dorsum of the distal phalanx permits visualization of the circulatory state of the finger.

A variety of techniques with plaster-of-paris immobilization were utilized and found to be satisfactory. It was advantageous to maintain the desired position during cast application by applying tape, moleskin, or collodion stripping from the palmar surface of the middle and distal phalanges, across the tip of the finger, and then with tension to the dorsum of the proximal phalanx. Subsequent to the cast application, the stripping was sectioned to release the excess tension. A beveled piece of felt was placed in the palm to maintain the hyperextension. With surgical repair, the cast applied permitted visualization of the distal phalanx and the attachment of the wire to the nail. In the closed cases the visualization was not found to be necessary.

Comparison with the phalangeal tubular plaster reveals the hand cast described to be obviously more cumbersome to the patient, and it has the disadvantage of interfering with hand function during the period of immobilization. We have never been impressed with the simplicity of application of the Smillie tubular plaster and believe application of the hand cast to be no more difficult. This fact is especially true with the anesthetized patient. With Smillie's technique of approximating the thumb to the finger, it is apparent that the tubular plaster cannot completely cover the flexor surface of the proximal phalanx when applied with this finger in the flexed position. This, undoubtedly, decreases the rigidity of the immobilization at the proximal interphalangeal joint. We have used the tubular plaster and have found it necessary to change it during the course of immobilization in most patients. This change could conceivably jeopardize the healing of the tendon in the event any change in position should occur during the procedure. Change of the hand cast has been unnecessary.

RESULTS

In a general orthopedic practice, 14 mallet fingers were treated in 11 patients over the past 5 years. No attempt was made statistically to analyze these cases with a prolonged follow-up. Those patients who were seen for a considerable period subsequent to treatment had no appreciable alteration of the results observed 4 to 6 weeks after immobilization was discontinued, the usual follow-up period. Eight fingers, all of which were seen more than 3 weeks after injury were treated by primary operative repair and

immobilization. Six fingers, all of which were seen less than 3 weeks after injury were treated by the closed method. Of the 6 treated by the closed method, only 5 were available for study as 1 patient did not return after the application of the primary cast. Two of the 5 patients treated without surgery required subsequent surgery because of the unacceptable results, thus raising the total of operative cases for study to 10. One of the 3 patients successfully treated by the closed method had a normal range of flexion and extension, and the other 2 had normal flexion and extension to better than 170 degrees.

All of the 10 patients treated surgically were improved to a worthwhile extent, possessing active flexion and extension of the fingers. Two had normal hyperextension, 3 extension to 180 degrees, 3 to approximately 170 degrees, and the remaining 2 to slightly less than 170 degrees.

In spite of permitting the pull-out wire suture to remain during the entire period of immobilization, no infections were encountered. None of the casts in the surgical group was changed until the entire period (5 weeks in this series) of immobilization had elapsed. One cast had to be removed in the closed series but this had been applied with pressure over the point of the avulsion. No residual disability was observed in the metacarpophalangeal joint from immobilization in flexion.

SUMMARY AND CONCLUSIONS

The authors believe that immobilization of the entire musculotendinous expanse in the relaxed position is a cardinal principle of tendon surgery and that this principle has been overlooked in the treatment of mallet finger injuries with phalangeal immobilization. They recommend the additional immobilization of the metacarpophalangeal joint in flexion. The anatomic rationale has been given and discussed. The innocent effect of prolonged immobilization in flexion on the metacarpophalangeal joint has been anatomically explained. A simple modification of the Bunnell pull-out wire suture for repair of tendon avulsions at the distal interphalangeal joint has been described and illustrated. A simple cast technique was described and compared with the tubular phalangeal cast. Roentgenographic visualization of approximation of the extensor mechanism subsequent to reduction and immobilization has shown the presence of a bone fragment accompanying the tendon avulsion. In a substantial percentage of mallet finger injuries treated by the closed method unsatisfactory results will be obtained. The incidence of excellent and satisfactory results subsequent to surgical repair indicates the merit of primary repair in the absence of roentgenographic visualization of approximation of the avulsed extensor mechanism.

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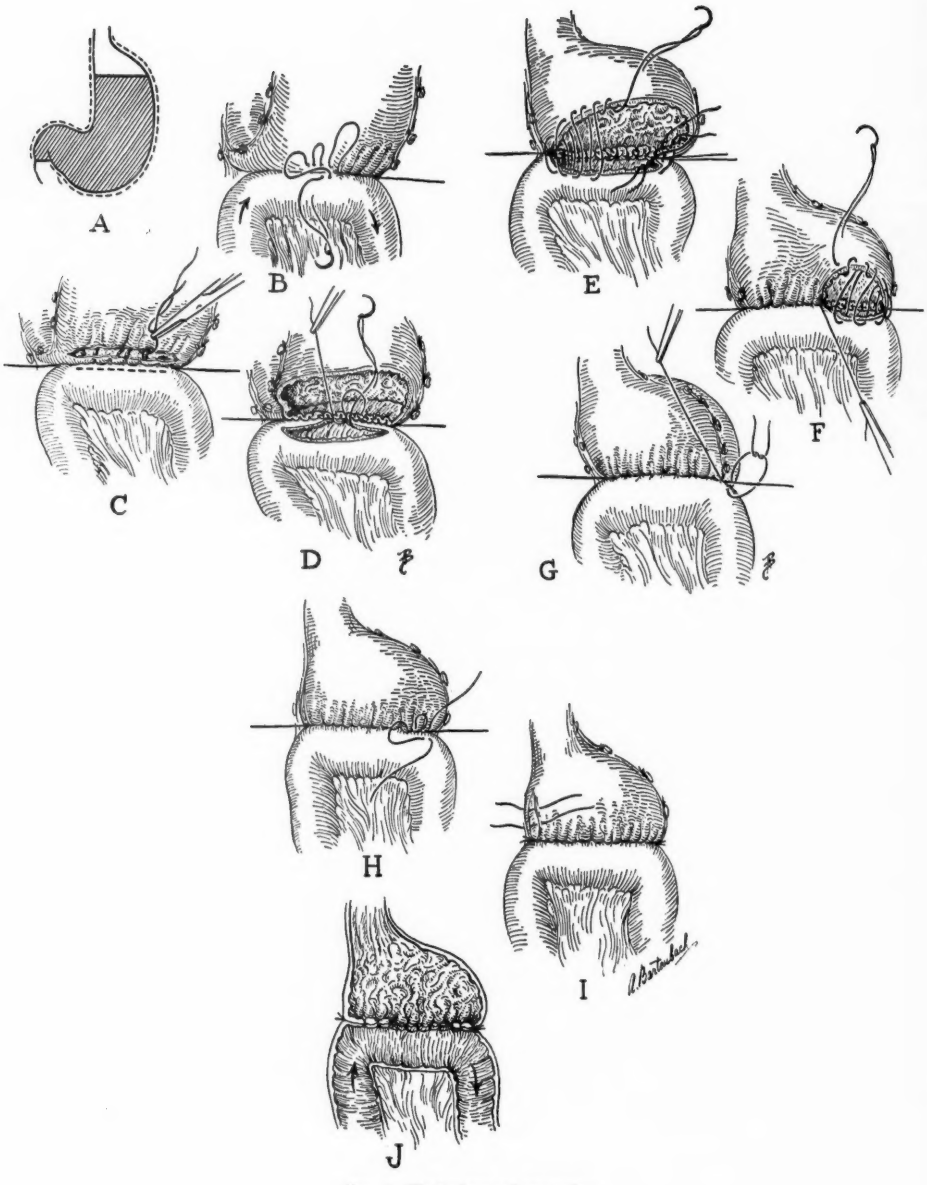

FIG. 1. Technique of operation.

A New Technique for Gastrojejunostomy with the Billroth II Operation.—William H. Myers and Morris T. Friedell.

A NEW TECHNIQUE FOR GASTROJEJUNOSTOMY WITH THE BILLROTH II OPERATION

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VARIOUS METHODS for re-establishing the continuity of the gastrointestinal tract following subtotal gastric resection have been developed through the years since the operation was first performed. Impetus was given to the development of technique as this operation became more popular due to its increased rate of survival and cure. The number of methods available is apparently limited only by the imagination of the surgeons performing the operation.

The ingenuity of the surgeons is exemplified in a review of the subject in 1940 by Polya in which he described no less than 37 different types of anastomoses.

Each surgeon develops a particular fondness for one type of resection because it works well for him, is technically easy, and fulfills the requirements necessary to relieve the patient of symptoms and avoid postoperative complications, immediate and late. It is apparent from the literature, however, that no one operation has as yet received universal acceptance as the ideal method.

The Polya operation remains popular with many surgeons who believe that it fulfills these requirements and is quickly and easily accomplished. Those who object to it believe that the large stoma permits rapid emptying of the gastric pouch which is responsible, at least in part, for postoperative dumping symptoms and other undesirable side effects. For example, it has been shown by Wallaeger and associates that patients with the Polya resection tend to lose more total fecal solids, fats, and nitrogen leading to a loss of weight unless an excess of fat is given in the diet. Possible factors contributing to this loss are rapid emptying, intestinal hyperperistalsis, diminished stimulation of secretion of bile and pancreatic enzymes, and imperfect mixing with these ferments. This tendency is noted less often, for example, with the Hofmeister type of Billroth II operation. The small stoma is mentioned frequently in this regard. MacLean and associates deny this fact and show experimentally that no correlation exists between rapid gastric emptying and loss of weight or increased fecal fat excretion.

Symptoms of dumping can be reproduced by the introduction of hypertonic solutions into the jejunum. It is believed that, in addition to the type of material used (notably carbohydrate), the amount and rapidity with which it is introduced are of great importance in starting this series of symptoms. Larger amounts would be released more quickly with a large stoma. In addition, the sphincter-like action developed at the stoma becomes more effective as the size decreases. Other objections include kinking of the proximal loop and edema of the suture line at the same point leading to varying degrees of obstruction of this limb. Jejunal distention and sagging opposite the stoma are also more common. In general then, most of the objections of the Polya procedure are considered to be the disadvantages of a large stoma.

We wish to present the technical aspects of a gastrojejunostomy modified from the standard Polya operation in which the size of the stoma is considerably reduced by continuous plicating sutures around the entire circumference of the anastomosis. This technique is somewhat similar to the Von Haberer-Billroth I operation, by which the entire cut end of the stomach is anastomosed to the duodenum. However, in this instance the disparity in the size of the lumen is compensated for by taking larger bites of stomach and occasionally by incising the anterior surface of the duodenum.

Our review of recorded techniques failed, however, to reveal any description of a similar method as applied to the Billroth II operation. Most of these are accomplished by closing off part of the

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FIG. 2. Barium meal, 8 months after operation.

gastric remnant separately to decrease the size of the stoma, as in the popular Hofmeister procedure.

TECHNIQUE

The stomach is mobilized in the usual way, the duodenum closed, and the left gastric artery ligated near its origin. It is very helpful to free the greater curvature entirely to the esophagus, releasing the fundus. This is done not particularly to remove more stomach but to better assess the size of the stomach and, therefore, the amount to be removed as well as to obtain more mobility for the anastomosis once the line of resection is chosen.

The short loop of jejunum is brought up anterior to the colon (posterior if desired) and applied to the posterior wall of the stomach at the proposed line of resection, distal limb to the greater curvature, and the posterior layer of continuous No. 000 silk is started as shown in Figure 1B. This seromuscular suture is continued horizontally taking 2 bites of stomach to 1 bite of jejunum each time and tied at the corner. Interrupted silk may be used for the seromuscular rows if preferred.

All large vessels presenting above this line of silk are now individually ligated with atraumatic catgut and the posterior wall incised distally (Fig. 1C). The posterior layer is then completed with continuous locked No. 00 catgut, the locked loop falling on the gastric side as in Figure 1D. Two separate sutures are used as illustrated, starting at the midpoint of the posterior wall. When the corners are reached, the stomach is removed and the bleeding points of the anterior wall are individually ligated. At each corner 3 or 4 interrupted catgut sutures are inserted to prevent plication in this area and the continuous sutures are then placed across the rest of the anterior wall, as in Figures 1E and 1F, taking all layers with 2 bites of stomach to 1 of jejunum and tied at the midpoint (Fig. 1F).

The anterior seromuscular row is of interrupted No. 000 silk and is started by placing the first stitch behind the tied end of the posterior silk, Figure 1G, to reinforce that angle. These sutures are continued across the anterior wall which is already partially infolded, taking 2 bites of stomach to 1 of jejunum, as shown in Figure 1H. The bare area of the lesser curvature is closed with interrupted silk sutures, Figure 1I, and another reinforcing suture is placed behind the tied end of the posterior row of silk, similar to Figure 1G.

Figure 1J illustrates this point and the appearance of the completed operation. When tested in the usual manner with the thumb infolding the jejunal wall and the fingers infolding the gastric wall, the stoma usually admits 2 fingers loosely.

The roentgenogram (Fig. 2) taken after a barium meal, approximately 8 months after surgery, shows the expanded gastric pouch and the function of the stoma.

One theoretical objection to this type of anastomosis is the possibility of bleeding from the anastomotic site due to the infolding of the gastric wall and its vessels. We believe bleeding can be avoided by ligating all vessels of the posterior and anterior walls as these layers are cut. As shown in Figure 1D, the posterior catgut layer is placed so that the locked loop falls on the gastric side rather than jejunal which further prevents bleeding from that layer. If rubber-shod clamps are used, they should be released before starting the anterior layer to check all bleeding points there. Another objection might be the possibility of leakage through the infolded area.

If the sutures are placed carefully with good serosal apposition, this seems unlikely nor was it observed in our cases. With this modification the stoma is decreased in size, the resection is high with a small remnant of lesser curvature, while the technical ease is not sacrificed nor compromised.

We present this additional method of gastrojejunostomy following gastric resection, not necessarily as an ideal but in the hope that it may be helpful in broadening the technical possibilities of all engaged in doing gastric surgery.

DISCUSSION

This technique was initially developed in dogs and was then performed on a series of patients of the Ward Service of Cook County Hospital. There were no mortality nor postoperative complications and the subjects have continued to do well in the short time following surgery. The procedure is still in use at this hospital and in private cases as well. No complications have been noted which could be directly related to the procedure.

The following case history will illustrate our immediate results:

W. L., a 43 year old Negro male laborer, married, was admitted to the Cook County Hospital on March 10, 1956 with the presenting complaint of severe burning epigastric pain, present intermittently for the past few years, during which time he had been given diets and several forms of antacids for "ulcer." The pain had been more and more persistent during the past 2 to 3 months, and he had received less relief from his medication. He had vomited on several occasions in the past few weeks with slight relief of pain. Hematemesis was denied but he was thought to have had several episodes of melena in the past 2 months. On 1 of these occasions, he suddenly felt weak, quit work, and later that day passed a large amount of black, tarry stool. Physical examination showed a thin, not acutely ill man. Blood pressure was 118/70; pulse 84, and temperature 98.6. Examination was negative except for slight tenderness in the epigastrium. Laboratory studies showed hemoglobin 80 per cent; urine was negative. Chest roentgenogram and electrocardiogram were normal. Stool benzidine test was negative. Barium meal showed deformity of the duodenal bulb, marked spasm, and mild retention. Peak free acid on histamine stimulation was 95 units. The patient was placed on milk-cream and amphojel, alternately every half hour, and was given belladonna, phenobarbital, multiple vitamins, and iron. On this regimen his symptoms subsided somewhat and he was soon given a general ulcer diet, had no vomiting, and began to gain weight. After 1 month of this regimen he was operated on. At surgery a fairly large posterior duodenal ulcer was found and a subtotal gastric resection was performed in the manner described. His postoperative course was uneventful and he was discharged on the twentieth postoperative day. Subsequently he has been seen frequently in the clinic. He has continued to do well, is back at work, and states he feels very well. No symptoms of dumping have been noted, and he has worked out a schedule of 4 meals a day.

SUMMARY

A technique of gastrojejunostomy after gastric resection is presented. The anastomosis is performed by plicating sutures around the entire circumference of the stomach wall, thus reducing the size of the stoma considerably. This is thought to be the first description of an anastomosis of this type applied to the Billroth II operation. A case report with postoperative roentgenogram is presented to illustrate the function of the stoma. The comparative advantages of this type of anastomosis are discussed.

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POSTOPERATIVE CHOLANGIOGRAPHY PARTIALLY PERFORMED WITH THE PATIENT IN THE UPRIGHT POSITION

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POSTOPERATIVE CHOLANGIOGRAPHY following cholecystectomy is a useful procedure to study the biliary system and adjacent structures before the removal of the T tube left in place by the surgeon. In the past, this examination was performed only with the patient in the recumbent position. However, during the last 5 years it has been found that additional observations made with the patient erect are of importance for the reasons to be discussed. The performance of postoperative cholangiography with the upright method has been possible by the use of a recently developed apparatus (Fig. 1).

DESCRIPTION

The apparatus (Fig. 1) is attached to the abdomen with an elastic nonopaque band which encircles the patient and is adjustable for circumferential dimensions by two buckles. Its flexible, thin metallic base is padded with sponge rubber. A glass syringe containing the opaque medium is maintained on an elevated table made of aluminum and padded with sponge rubber. The plunger is controlled by a metallic ratchet. The syringe holder can be moved in any desired position and held by a locking device.

TECHNIQUE

The apparatus is placed over the right anterior lower part of the abdomen (Fig. 2) and kept in this position throughout the entire examination. The T tube is then connected to the syringe by a metallic adapter which has a three-way stopcock. Another empty syringe is connected to the upper opening of the stopcock and the fluid and air contained in the tube and the biliary tree are gently aspirated until the T tube collapses. After aspiration, the second syringe is removed, and 2 to 4 cubic centimeters of opaque medium are slowly injected under fluoroscopic control. A slight aspiration of fluid is made by the syringe containing the opaque medium in order to confirm the continuity of fluid and to remove any remaining air bubbles. Serialographic views of the distal common bile duct are taken with the patient in the right posterior oblique recumbent position following the introduction of 0.5 cubic centimeter of opaque medium before each exposure. Additional larger exposures are then obtained using the same apparatus and the Trendelenburg position to demonstrate the entire system and, specifically, its proximal part. In order to take the upright films, the table is brought to the erect position and under fluoroscopic control a spot serialographic film of the distal common bile duct and one larger flash film are taken. Five to 15 cubic centimeters of 50 per cent opaque medium are usually considered to be sufficient for an average patient.

DISCUSSION

In the last 5 years no accidents, allergic reactions, or other sequelae have occurred in performing postoperative cholangiography with this method. For precautionary reasons, older and extremely weak patients are examined while they are in the recumbent and semierect positions.

Heavier water soluble solutions are preferred to the previously used 35 per cent solution of opaque media for the following reasons: (1) Heavier opaque media (50 per cent water soluble) permit better visualization of the system during fluoroscopy and produce sharper contrast on the roentgenograms with smaller amounts. Thus, overfilling of the system, obscuring stones or other abnormalities and causing discomfort to the patient, is avoided. (2) The anatomy and physiology of the system is not significantly changed. (3) The function of

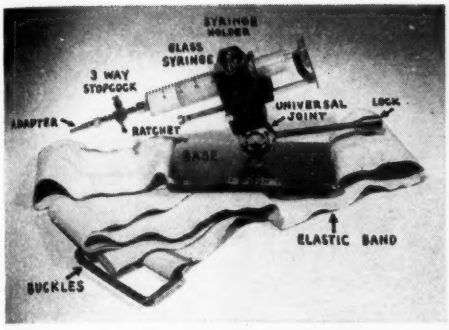

FIG. 1. Photograph of apparatus.

sphincter of Oddi and the intraduodenal part of the duct and their abnormalities can be better studied. If persistent spasm of sphincter of Oddi is present, the use of nitroglycerin has resulted in more effective relaxation than introduction of spasmolytics within the system.

Double contrast studies of the distal common bile duct with the patient in the Trendelenburg position have been unsuccessful because the opaque media presently used form bubbles with the introduced air.

The advantages in performing postoperative cholangiography with the described method and apparatus are as follows:

1. Since the apparatus is firmly attached to the patient, fluoroscopic observations may be performed and films may be taken in any position. Particularly valuable are studies in the erect position in which the distal common bile duct unfolds so that its intraduodenal part can be better visualized (Fig. 3). Unusual kinks and contractions of the distal common bile duct can be better evaluated in the same position. Differentiation of nonopaque gallstones from air bubbles can be easily made. Air bubbles will disappear from the distal bile duct when the patient is moved from the recumbent position, whereas gallstones remain (as can be seen in Figs. 4 and 5).

2. Nonsterile materials are not used to hold the syringe in place.

3. No needles are used at any time for aspiration and emptying of the biliary system or injection of opaque medium. Therefore, there is no danger of injuring the patient or of loss of opaque medium due to penetration of the T tube by needles.

4. Better control of the amount and rate of flow of the opaque material results in elimination of air bubbles.

5. Considerable economy of time and increased

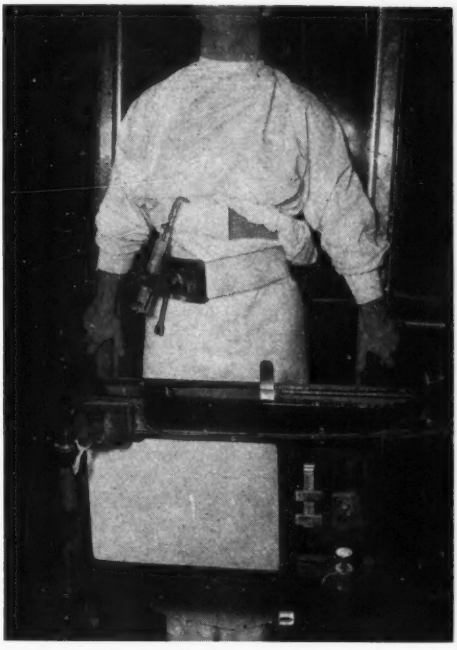

FIG. 2. The apparatus and its application with the patient erect.

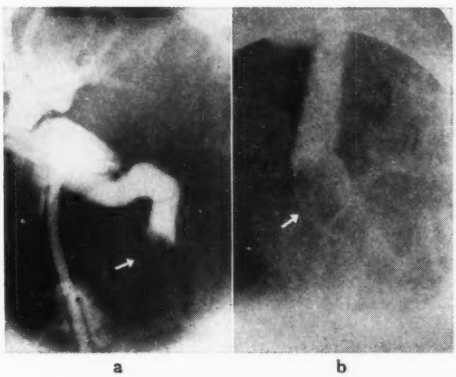

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FIG. 3. a, Roentgenogram made with the patient in the right posterior oblique recumbent position showing an irregular filling defect in the distal bile duct. b, Roentgenogram of the same patient in the left anterior oblique erect position, showing the presence of a large gallstone not well outlined in "a."

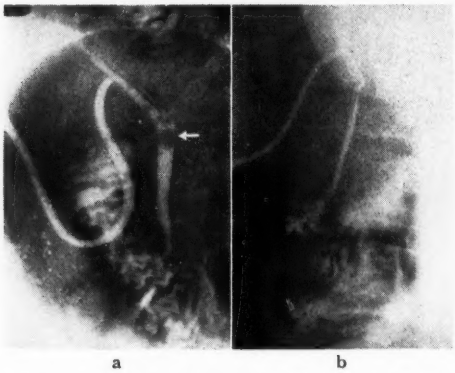

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FIG. 4. a, Roentgenogram made with the patient in the right posterior oblique recumbent position showing air bubbles in the common bile duct. b, Roentgenogram of the same patient in the erect position showing disappearance of the air bubbles, better demonstration of the distal bile duct, as well as visualization of the pancreatic duct.

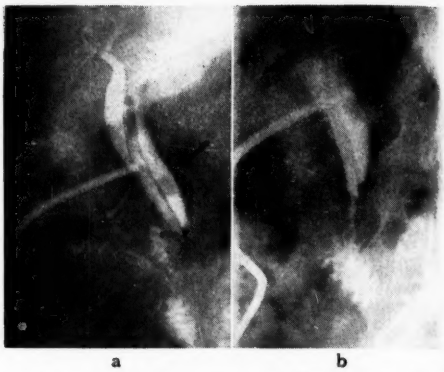

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FIG. 5. a, Roentgenogram made of the patient in the right posterior oblique recumbent position showing a large radiolucent gallstone within the distal common bile duct. b, Roentgenogram of the same patient in the left anterior oblique erect position showing the radiolucent gallstone remaining in the common bile duct. Better visualization of the distal common bile duct is achieved.

availability of space are achieved, since the patient can be moved to another room with the apparatus in place while the films are being developed. The entire roentgenographic examination of the patent may be performed within a few minutes.

6. Repeated examinations have been avoided because of the more conclusive results obtained with this method.

SUMMARY

The performance of postoperative cholangiography by a satisfactory method with a new apparatus has been described. Examination of the patient in the erect position is advantageous in evaluating the appearance of the distal common bile duct. Air bubbles are easily differentiated from calculi on films taken with the patient in this position.

The Book Shelf

EDOARDO PORRO AND CESAREAN HYSTERECTOMY

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CESAREAN SECTION, until the latter part of the nineteenth century, was regarded as one of the most hazardous of obstetric operations, to be undertaken only as a last resort. The operation was carried out 80 times in the United States before 1878, with a maternal mortality of 52.5 per cent. Not a single cesarean section was performed among the first thousand confinements in the Sloane Maternity Hospital from January 1, 1888 to October 1, 1890 (6). Abdominal hysterectomy, likewise, achieved medical respectability only in the closing decades of the last century. The earlier attitude toward this operation was epitomized editorially in the London Medico-Chirurgical Review of 1825 (4): "A more cruel, bloody, and ill-judged operation is not, we think, recorded in the annals of surgery . . . . We consider the extirpation of a uterus not previously protruded or inverted, one of the most cruel and unfeasible operations that ever was projected or executed by the head or hand of man." Before 1863 abdominal hysterectomy had proved fatal in seven-eighths of the patients on whom it was attempted; only in 3 cases had it been performed successfully in the United States. Cesarean hysterectomy becomes something of a paradox, therefore, when viewed in historical perspective, for it evolved from efforts to circumvent the mortal danger of abdominal delivery by the addition to it of a similarly formidable procedure, uterine extirpation.

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The history of cesarean hysterectomy dates back to 1768, exactly 100 years before it was first carried out in the human, when Joseph Cavallini successfully excised the pregnant uteri of dogs and sheep, proving that the organ was "not at all necessary to life," and speculated that a more fortunate generation would demonstrate that the womb "may be plucked out with impunity from the human body." The background of cesarean hysterectomy has been recorded by J. H. Young in his monograph on the history of cesarean section. In 1809, Godofried P. Michaelis suggested that the great danger of cesarean section might be ameliorated by combining with it amputation of the uterus, but there is nothing to indicate that Michaelis ever made such an attempt himself. Similar thoughts were voiced by others. James Blundell, for example, in his obstetric lectures at Guy's Hospital stated in 1827: "In speculative moments I have sometimes felt inclined to persuade myself, the dangers of the Caesarean operation might, perhaps, be considerably diminished by the total removal of the uterus." Blundell's efforts to test his hypothesis were limited to rabbits, however; others continued to experiment on bitches.

The first cesarean hysterectomy on a woman was performed on July 21, 1868 by Horatio Robinson Storer. Storer was born in Boston in 1830, the son of David Humphreys Storer, successor to David Osgood as Director of the Boston Lying-in Hospital (5). After receiving his degree from the Harvard Medical School in 1853,

FIG. 1. Edoardo Porro (1842-1902).

young Storer went abroad to continue his training in Paris and London and to work with the great James Young Simpson in Edinburgh. Upon his return to Boston in 1855 he entered general practice, but ever a nonconformist, he broke with prudish Bostonian tradition in 1862 by announcing himself a specialist in the diseases of women. He subsequently became the first American physician to teach gynecology as a separate subject. He was also the first surgeon to wear rubber gloves while operating. In 1866 Storer's sturdy independence resulted in his removal from the Harvard faculty. In this same year he performed the fourth successful abdominal hysterectomy in America, removing a myomatous uterus weighing 37 pounds.

Heartened by the happy outcome of this case Storer was emboldened to resort to hysterectomy again 3 years later to stanch the hemorrhage from the uterus during a cesarean section. Storer had posted a milestone in obstetric history—but unwittingly, it would seem, for he did not even deem the event worthy of recording himself, and it remained for his assistant, G. H. Bixby, to report the case before the Boston Gynaecological Society.

The patient, aged 37 years, consulted Storer on July 16, 1869, "for pregnancy complicated by a large obscure abdominal tumor." The tumor blocked the pelvis to such a degree that Storer predicted vaginal delivery of the infant would be impossible, even with craniotomy. He instructed the patient to notify Dr. Bixby at the onset of labor. "Two days afterwards," Bixby narrated, ". . . being out of town, I was telegraphed for, in great haste; from some mistake the message did not reach me for twenty-four hours. Upon my arrival . . . I found the patient suffering from slight pains, the water having passed off some hours previously. By vaginal examination I found the cervix dilated to the size of a dime-piece. Having got the finger past the point of obstruction by the tumor, there was not the least difficulty in detecting the foetal head, which presented still very high up, pressing upon the tumor from above . . ."

After consultation the next day among Professor D. H. Storer, Dr. H. R. Storer, a Dr. Warner, and himself, Bixby continued, "it was decided to leave the case for some little time to the natural powers. I spent the night with the patient, during which she had . . . slight pains. Examination, however, revealed nothing new, and in the morning so completely in statu quo was the condition of everything, that I even doubted the fact of her being in labor at all. In the morning Dr. H. R. Storer saw the case again, and having satisfied himself that no progress whatever had been made, owing entirely to the presence of the tumor, and that this condition would continue, so far as any efforts on the part of nature were concerned, decided to proceed upon the following day to an abdominal section as the only possible chance of saving the mother's life.

"July 21st . . . the patient was placed under the influence of chloroform, another examination made, and the following conclusions were definitely arrived at: 1st, that there was present, pregnancy complicated either by a fibro-cystic tumor of the uterus, or a multilocular ovarian cyst, with one of its appendages crowded down between the pelvis and the uterus; 2d, that even with mechanical interference the escape of the foetus per vias naturales was utterly impossible; 3d, that the space between the tumor and the pelvic wall, being less than one and a half inches, would not admit either of craniotomy, cephalotripsy, cranioclasm, or any other mechanical interference per vaginam; and, 4th, that Caesarean section . . . was certainly indicated as the only resort, provided it were impossible to remove the tumor by abdominal section, and then proceed to a forced labor.

". . . Upon cutting through the peritoneum there presented a large, smooth, bluish-colored tumor, which might have been taken either for the impregnated uterus, a discolored cyst of the ovary, or a fibrous tumor. . . . Exploration with the hand within the abdomen established the existence of a fibro-cystic tumor of the left and lower anterior wall of the uterus, with an outgrowth nearly the size of the foetal head, originally pediculated, but now firmly adherent low down to the walls of the pelvis. On the right the uterus, with the foetal members plainly to be felt through its walls, was perceptible, but so retroflexed as to render it very difficult to cut into at this point.

"An exploratory incision was now undertaken in the tumor situated at the left. Each stroke of the knife revealed a regular series of concentric layers of fibrous tissue, not unlike that of the uterus. After cutting down to the distance of about two inches, the scalpel glided suddenly into a cavity, filled with a thick, brown, semi-fluid, putrilaginous substance, evidently resulting from degeneration of the fibroid. The hemorrhage being already very profuse, and the danger from shock and exhaustion imminent, with a few rapid strokes of the knife, Dr. Storer extended his incision into the cavity of the uterus, and with all expedition removed a male child, weighing eight pounds; it being, as well as the placenta, in an advanced state of decomposition . . . . There was little time to be lost, for the hemorrhage from the incision into the vascular structure of the uterus, together with the open vessels at the site of the placental insertion . . . was perfectly frightful. It was apparent that the tumor in the uterine wall would necessarily prevent a perfect contraction of the organ, and thus render suppression of the hemorrhage impossible, contrary to what obtains in ordinary uncomplicated cases of Caesarean section.

"With his usual self-possession, Dr. Storer decided to remove the whole mass as far as possible. . . . Accordingly, a large-sized trocar having been passed through the upper segment of the cervix uteri, and a metallic cord passed doubled through its canula, the whole was firmly tied in two parts. Fearing lest this constriction might not prove sufficient to check the hemorrhage from so vascular a part, especially the pedicle of the pelvic tumor, which was included in the ligature, the ecraseur with its chain outside the canula . . . was applied, and

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Dell'amputazione utero-ovarica come complemento di taglio cesareo; pel *dottore* EDOARDO PORRO, *Professore ordinario di Ostetricia e Ginecologia nell'Università di Pavia.*

I progressi rilevantissimi della chirurgia in generale e quelli assai splendidi della ginecologia e dell'ostetricia, non hanno portato sensibili miglioríe nell'esecuzione e nell'esito di quella grande operazione che è il taglio cesareo.

Gli è perciò che oggi, come per l'addietro, il taglio cesareo è considerato una operazione formidabile, temibile, una estrema risorsa dell'ostetricia, una dura necessità, riservata fortunatamente a pochissimi casi.

Il diagnostico esatto dei tumori uterini e pelvici e la loro cura razionale, la pratica diffusa del parto prematuro e quella pure sancita dell'aborto provocato, hanno tolto un grande, il massimo contingente di casi, che altra volta forzavano, con malaugurata frequenza, ad aprire il ventre a tante meschine, cui ben di rado la morte risparmiava.

Epperò, se il numero dei casi indicanti il taglio cesareo è al presente assai limitato, anche in grazia alla migliorata istruzione teorico-pratica dei medici e delle levatrici, pure il risultato della gastro-isterotomia non ha cambiato gran fatto e tutti gli ostetrici moderni son convinti di risparmiare tanto pericolo alla donna, quando altre risorse, compresa quella del sacrificio

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FIG. 2. Title page of Porro's paper reporting his case of cesarean hysterectomy.

the mass slowly constricted. Having been removed, its stump was held by the ligature, and seared by the hot iron. Not feeling even then secure against a recurrence of hemorrhage, Dr. Storer applied his clamp-shield, which controlled the pedicle completely. Everything now being perfectly safe, without the least hemorrhage persisting, the abdomen was carefully cleansed of all coagula, and the wound brought together by ten deep silver sutures, which involved the peritoneum. . . The operation was commenced at half-past twelve M., and terminated at half-past three, P.M." The patient recovered from the effects of the chloroform and "returned to consciousness in the happiest way, without complaining of the least pain or discomfort." The following day she began to fail, however, and succumbed on the third postoperative day. "It was a matter of surprise to all concerned," commented Bixby, "in view of the terrific character of the operation, that she should have survived it at all, and still more for so long a time."

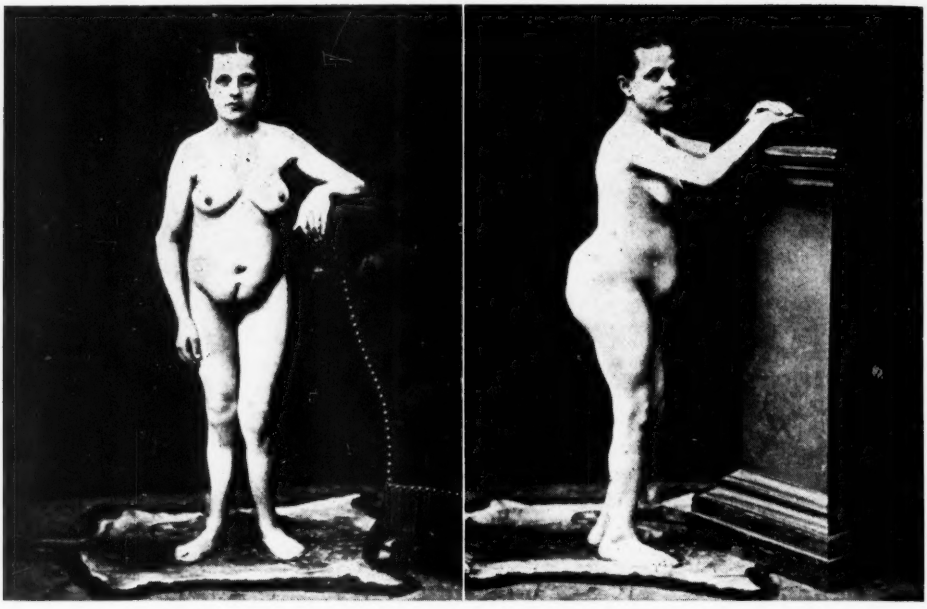

FIG. 3. Plate from Porro's paper showing Julia Cavallini after her convalescence from cesarean hysterectomy.

Seven years elapsed before the next cesarean hysterectomy. In contrast to Storer's hasty decision to proceed with amputation of the puerperal uterus as a lifesaving hemostatic measure in a patient who had been in labor for 3 days, his 3 hour operation, his apparent failure to appreciate the significance of his feat and his unconcern with its publication, and the fatal outcome to both mother and child, the operation performed by Edoardo Porro of Pavia, Italy, on May 21, 1876, was a carefully planned and rehearsed procedure carried out in 26 minutes under optimal conditions with survival of both patients. Porro, moreover, sensing the importance of his achievement, the first successful cesarean hysterectomy, publicized it in a report of 63 pages. The operation has since been known throughout the world as the Porro operation.

Until the time of Porro, cesarean section had suffered a particularly bleak record in Pavia, no woman ever having survived the operation in that city. On April 27, 1876, a 25 year old primigravid dwarf, Julia Cavallini, was referred from the general hospital of Pavia to Porro's obstetric clinic in the University because of the suspicion of a malformed pelvis. The patient's surname, by coincidence, was the same as that of the experimenter who, a century earlier, had predicted that extirpation of the gravid uterus would one day be carried out safely in women. Between the ages of 3 and 10 years the patient had suffered from rickets, and during this period was unable to support herself in the erect position without help. The resultant skeletal deformities were partially corrected in later years, and she became married to a teacher of dramatics. Her last menstrual period, a matter of some uncertainty, was recorded as mid-July 1875.

She was 148 centimeters tall and presented the typical bony stigmas of rickets, including saber shins, knock-knees, bowlegs, enlarged joints, and scoliosis. The right iliac crest was 4 centimeters higher than the left. Obstetric examination revealed a normal intrauterine pregnancy at term, the vertex floating, and the fetal heart best heard in the left lower quadrant of the abdomen. The retropubic and subpubic arches were very narrow, the sacral promontory was very prominent and deviated to the right, and the pelvis narrowed transversely as well. The diagonal con-

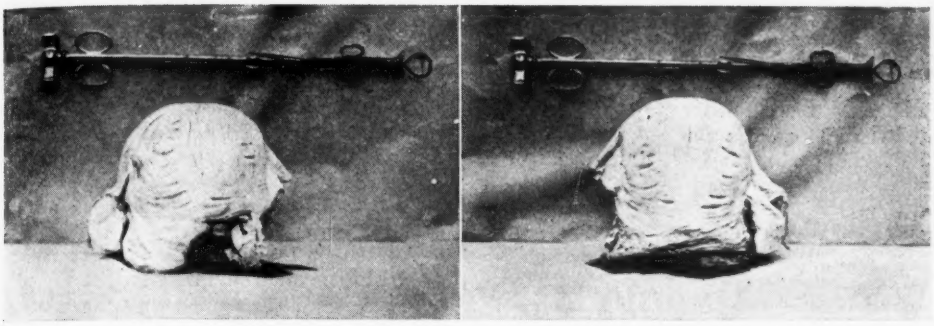

FIG. 4. Plate from Porro's paper showing the excised uterus and adnexa together with the snare of Cintrat.

jugate measured 7 centimeters. In addition, the superior strait was overhung by the spondylolisthesis of the lumbar vertebrae which formed a sort of roof over the pelvic inlet.

"It was obvious," Porro wrote, "that absolute disproportion existed and that cesarean section was mandatory." He therefore called a consultation with a group of his colleagues, gravely pointed out the impossibility of vaginal delivery or even embryotomy and that no alternative to cesarean section existed; and all solemnly concurred. Prolonged discussion followed concerning the location of the uterine incision and the methods for coping with the anticipated hemorrhage, some of the consultants even advocating inversion of the uterus after its evacuation, to be followed by vaginal hysterectomy. Tacit consent was finally given to Porro's proposed plan to amputate the uterus through the abdominal incision if serious hemorrhage were encountered after delivery of the infant.

The patient was admitted to the hospital in anticipation of labor, which began at 10 a.m., May 21, with rupture of the membranes. The patient's predicament was explained to her, but operation was deferred while she sought religious support. "I did not press the matter until 4 p.m.," Porro recounted. "By now the pains were quite strong, and these alone sufficed to persuade the patient to accept our advice. . . . At 4:40 p.m. she was taken to the obstetrical amphitheatre, which had been heated to 18° C. Everything was in readiness. . . . To avoid confusion, all the assistants had been carefully instructed in advance, each as to his own duty. . . . At 4:42 p.m. the chloroform anesthesia was begun . . . and the amphitheatre was rapidly filled with a large number of physicians and students. . . .

"At 4:51 p.m. we began to cut through the abdominal wall, layer by layer, through a 12 cm. incision in the linea alba. . . . After the peritoneal cavity was opened . . . the uterus was immediately incised, in the same direction and to the same extent as the abdominal incision. . . . Unable to deliver the fetal head with my right hand in the uterus, I finally reached up, grasped and delivered the right leg and thigh; the left leg, trunk, arms, and head followed immediately. We extracted a large [3,300 gram] female infant, alive, healthy, well formed, and crying spontaneously. After tying and dividing the umbilical cord we proceeded to extract the placenta, which was removed intact, together with the major portion of its membranes. . . .

"The uterus bled from its cut edges. We brought the organ out through the abdominal incision, and with our fingers we compressed the points that were bleeding most vigorously, but adequate hemostasis could not be obtained." Attempts to control the bleeding by suture were also unsuccessful and finally abandoned. "It was providential," Porro remarked, "that we had made all the preparations necessary for hysterectomy; otherwise the patient would surely have died.

"Holding the uterus up out of the abdominal wound . . . we placed the strong wire snare of Cintrat at the level of the internal os and drew it very tight . . . winding it also around the left ovary, to hold the wire up and keep it from slipping down over the lower end of the cervix . . . . After we ascertained that the blood flow was completely shut off, we excised the uterus

above the ligature . . . the constricted stump remaining within the ligature. . . . With the index finger of the right hand in the vagina, a large curved clamp was introduced through the left side of the cul-de-sac into the peritoneal cavity, the left hand serving as a guide. A 5 mm. drainage tube was thus drawn down into the vagina from the peritoneal cavity.

"We proceeded immediately with the peritoneal toilet. After removing two small blood clots and cleansing the uterine stump, we noticed a small ovarian cyst, the size of a small nut, attached by a long thin pedicle to the part of the left ovary distal to the ligature. With a fine thread we excised this tumor distal to the ligature. . . . Suture of the abdominal wall was accomplished with a strong, pliable silver wire . . . only four sutures being necessary for perfect approximation." The uterine stump was incorporated into the lower angle of the wound by means of the lowermost suture and painted with iron perchloride. The snare and handle were allowed to rest between the patient's legs. Thus was completed the first successful cesarean section in the city of Pavia and the first successful cesarean hysterectomy in history.

The patient's postoperative course was marked by vulvovaginitis, decubitus ulcers over the sacrum, suppuration at the lower end of the abdominal wound, and a urinary tract infection, but was characterized by Porro as "uneventful," for such trivia were completely overshadowed by the fact that the patient had indeed survived. The snare was removed with the gangrenous portion of the uterine stump on the fourth day after operation, and the sutures 2 days later. The vaginal drain was withdrawn the following week when Porro pronounced the abdominal wound "most beautiful and almost completely healed."

A long discussion concerning the morality of the operation was subsequently held with the Bishop of Pavia, who sanctioned the hysterectomy as a procedure for saving the patient's life. With this ecclesiastic backing, Porro stated before the Medical Congress of Turin: "I believe that the day is not far off in which medical science will pronounce its solemn verdict approving utero-ovarian amputation in every case of cesarean section." During the ensuing years the operation was indeed adopted in many centers as the standard procedure in cases of abdominal delivery, with a dramatic reduction in the maternal mortality resulting. Since Porro's day the indications for the operation have undergone much change, but cesarean hysterectomy continues to be known as the Porro section.

Edoardo Porro, the son of an engineer, was born in Padua, September 17, 1842 (3). After obtaining his medical degree from the University of Milan in 1865 he embarked on a course of postgraduate training at the Hospital Maggiore, but soon forsook his studies there to fight for Italian unification under Garibaldi. In 1871 he was made Director of the School of Obstetrics in his alma mater, and 4 years later was appointed Professor of Obstetrics in the University of Pavia where he remained until 1882, when he returned to Milan as head of its obstetrical department. In Milan, Porro displayed a talent for hospital administration, helping to organize an anatomic institute and a surgical hospital. In addition to his professional activities, he maintained an active interest in a liberal form of government, and in the year 1891 was elected to the Italian Senate. Porro died on July 20, 1902.

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Reviews of New Books

As presented in the 1956 edition, the *Collected Papers of the Mayo Clinic and the Mayo Foundation*[1] provide a further record of medical experience of noteworthy value to doctors. The book emphasizes clinical rather than laboratory findings and presents many practical problems and answers in the field of practice. This is possible because the number of patients attending the Clinic and the extensive variety of their medical and surgical conditions favor the study of large series of cases. Thus there is provided a suitable basis for the evolution of new concepts in some diseases and for strengthening already proved principles in more familiar fields.

This fact is demonstrated in the section dealing with brain, spinal cord, and nerves. Here considerable space is provided for the presentation and interpretation of electroencephalography in a new dimensionable approach in brain wave recording. Another recent advance is discussed in order to present some firsthand knowledge of the clinical use of electromyography in diseases affecting nerves and muscles. For the psychiatrist and practitioner who are engaged in the care of the depressed or hypertensive patient, there is a brief on experiences with Rauwolfia compounds and a warning regarding its use. On the other hand a useful reminder to all clinicians is found in an article by a senior member of the department of neurosurgery which emphasizes the frequent failure to recognize intraspinal tumors as a cause of pain and disability.

As would be desired in a collection of treatises concerned with modern medicine, a large section deals with methods available in the diagnoses and surgical treatment of some defects of the heart and great vessels. Experience is summarized and some results are presented. It is evident that although problems remain there is increasing encouragement for workers in this field because real advances are being made. For the patient who a few years ago was an impossible therapeutic problem, there is now reasonable prospect for improvement or cure.

The papers on ductless glands contain most excellent descriptions of a number of diseases affecting the thyroid gland. The role of radioactive iodine when it is employed in tests of thyroid function and its indications and limitations as a therapeutic means are considered.

The authors dealing with the digestive tract present no new information. There is a complete description of operative cholangiography, a procedure gradually receiving wider acceptance. However, all contributions are composed of solid information based upon wide experience and judgment developed over a period of many years. These sections serve as excellent references and sources of information.

—*K. R. Trueman.*

[1]Collected Papers of the Mayo Clinic and the Mayo Foundation. Edited by Richard M. Hewitt, M.D., and others. Volume 48, 1956. 778 pages, illustrated. $12.50. Philadelphia and London: W. B. Saunders Co., 1957.

The concisely written monograph *Les accidents circulatoires du cerveau*[2] could be used as a practical guide in the diagnosis and treatment of the commoner problems of intracranial vascular disease which confront the neurosurgeon. The authors' methods of diagnosis and the reasons for any surgical procedures would be accepted as sound and workable by most American neurosurgeons, and the authors' opinions are evidently based upon an extensive clinical experience. They point out the tumor-like clinical picture of the old intracerebral hematoma and detail the necessary diagnostic steps as: thorough neurologic examination, retinoscopy, lumbar puncture (rarely either useful or advisable), electroencephalography, ventriculography, and arteriography. The surgical evacuation of the clot must be undertaken just as early as diagnosis can be made, be the clot recent or old, and this is all the more true in the patient who is gravely ill. Of course, in the obviously premortem patient, or in the one showing rapid spontaneous recovery, surgery should be withheld. The same general rules apply in the surgical treatment of extracerebral hemorrhage. The usual sources of both intracerebral and meningeal space bleeding are enumerated.

The authors have been impressed by the damage which a large soft and necrotic area of brain tissue may lead to, and advise its early removal by direct suction. Such lesions are a classical result of ischemia. The diversity of causes and of types of ischemic lesions makes it difficult to systematize treatment, but the authors have had some success with carotid thrombectomy when thrombosis of that vessel was the lesion. Novocainization of the stellate ganglion, stellectomy, carotid arteriectomy or ligation, carotid-jugular anastomosis, and pericarotid sympathectomies comprise the surgical possibilities, each to be applied more according to the enthusiasm of the surgeon than because of any proved specificity of the operation.

—*John Martin.*

Using the meningioma as an example, the authors of the book entitled *Les meningiomes*[3] emphasize that it was through the skills acquired in tumor surgery that many of the current possibilities in "latter day neurosurgery" have become realities. They speak with the authority of wide experience, conducting, as they do, the neurosurgical service of the famous old Salpêtrière. In the past 15 years they have operated upon 2,600 intracranial tumors, 340 of which were meningiomas (the basis of this report), with an additional 70 spinal meningiomas. Trauma is believed to be a definite etiologic factor.

The section on differential diagnosis by mechanical means is practical and is clearly presented (radiog-

[2]Les accidents circulatoires du cerveau; traitement chirurgical de l'hemorragie et de l'ischémie. By J. Guillaume, G. Mazars, R. Rogé, and A. Pansini. 141 pages, illustrated. Paris: Presses Universitaires de France, 1957.

[3]Les méningiomes; étude clinique et chirurgicale. By J. Guillaume, R. Billet, J. P. Caron, and D. Cuccia. 173 pages, illustrated. Paris: Presses Universitaires de France, 1957.

raphy, air studies, arteriography, electroencephalography). Using the globus classification of meningiomas, the anatomic-clinical characteristics of each type are described, together with the surgical techniques specially applicable. These techniques are those time-honored and generally accepted everywhere. The authors are particularly concerned with the importance of anesthesia, apparently not employing some of the more recent, improved (questionable) methods. On the day previous to operation, the patient is medicated with barbiturates; at operation, he is intubated under pentothal curare and carried on a closed system with protoxide, ether, and oxygen, using additional intravenous pentothal sodium as necessary. Every precaution is taken that the patient remain relaxed, that pulmonary ventilation be adequate, and that there be no carbon dioxide retention.

Results of surgery on the spinal cord are usually gratifying, being almost directly proportional to the length of time that the cord compression existed, i.e., with diagnosis and surgical removal.

This monograph is exceptionally well illustrated, and the extensive bibliography is up to date. The authors are to be congratulated on this lucid, brief, yet complete discussion of meningiomas from the standpoint of the practicing neurosurgeon.

—*John Martin.*

TOXEMIA OF PREGNANCY has been described as a disease of theories, and this observation is well illustrated by Theobald's recent contribution[4] to the subject. The author is an experienced, recognized investigator who has devoted much of his life in an attempt to unravel this knotty problem. He knows his subject and presents an excellent review of much of what has been written, setting forth both the pros and cons on controversial attitudes. The bibliography at the end of each chapter is extensive.

The book is well written in the witty, erudite style of the educated Englishman, and is divided into 4 parts. In the first part, the author shows that pregnancy borders on the pathologic for the individual, and that profound metabolic and hormonal changes occur associated with a new gland, the placenta. In part 2, it is shown that in many respects healthy pregnancy is associated with trespass beyond the boundaries of the physiologic and that eclampsia represents but an exaggeration or modification of these trends. In part 3, the various theories of eclampsia are examined and the author then proceeds to develop his nutritional-mechanical hypothesis. In part 4, therapy is presented without specific recommendations other than prevention.

The reviewer is completely satisfied that this is one of the finest documents written on the subject, from bibliography to typography. His only wish is that more attention had been given to therapy, particularly to the newly revised hypotensive therapy which is beginning to emerge as one of the very real contributions to obstetrics in the past decade.

—*Edwin J. DeCosta.*

[4]THE PREGNANCY TOXEMIAS OR THE ENCYMONIC ATELOSITESES. By G. W. Theobald, M.A., M.D. (Camb.), F.R.C.S. (Edin.), F.I.C.S., F.R.C.O.G., M.R.C.P. (Lond.). 488 pages, 56 illustrations. $15.00. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1956.

IN THE BOOK entitled *Gerichtliche Geburtshilfe*[5] the author has covered every aspect of forensic medicine. In the 12 chapters the following subjects are presented: legal questions about birth, legal interruption of pregnancy, criminal abortion, infant deaths, trauma and gestation, unexpected sudden death during pregnancy, labor, and puerperium, paternity, the physician's duty of secrecy in obstetrics, permission for and explanation of obstetric manipulations, so-called "lack of skill" in obstetrics, mistakes and errors in obstetrics and their punishment, and the obstetrician in court (as expert consultant, witness, and defendant). A book of this type is indispensable not only in Germany but also in the United States where lawsuits against obstetricians (and other physicians) have been filed in frightening numbers during the last few years.

The book is very well written in simple language with a minimum of the legal terminology which is sometimes confusing to physicians. Of course, the author enlisted the aid of legal advisers. At the end of the book is a stupendous number of references, practically all of which are German. While the laws in Germany and the United States differ in many respects, this book nevertheless will prove of great value to all who practice obstetrics.

—*J. P. Greenhill.*

THE VOLUME *Anatomie et chirurgie du péricarde; applications à la chirurgie broncho-pulmonaire*[6] is the only complete work in French on this subject. The first part, Anatomy, is the description of the serous and fibrous pericardium and its relationship with the heart, pleura, lungs, diaphragm, and the great vessels, its vascularization and innervation. The second part is devoted to surgical techniques: various approaches to the pericardium, pericardiocentesis, drainage, pericardiotomy, pericardiectomy, removal of cysts and tumors, cardiopericardiopexy, transpericardial approach to the bronchi, and ligature of pulmonary vessels. The authors also discuss the pericardium in relation to surgery of the ductus arteriosus.

This book certainly should be of interest to thoracic surgeons. Several new techniques are described, and the illustrations are excellent.

—*Martin Laberge.*

THE NATIONAL CANCER CONFERENCE was designed to unify the differing views on the cancer problem. It was planned to expose the clinician to the experimental research worker and vice versa so that each might realize the importance of the other side of the picture. In the *Proceedings of the Third National Cancer Conference*[7] it is evident that this hope has been accomplished.

[5]GERICHTLICHE GEBURTSHILFE. By Prof. Dr. H. Naujoks. 247 pages, not illustrated. $6.40., D.M. 27 ($6.40). Stuttgart: Georg Thieme Verlag, 1957.

[6]ANATOMIE ET CHIRURGIE DU PÉRICARDE; APPLICATIONS A LA CHIRURGIE BRONCHO-PULMONAIRE. By Henri Milhiet and Paul Jager. Preface by J. Baumann. 292 pages, 145 illustrations. 4,000 fr. Paris: Masson et Cie, 1956.

[7]PROCEEDINGS OF THE THIRD NATIONAL CANCER CONFERENCE; DETROIT, MICHIGAN, JUNE 4-6, 1956. Sponsored by the American Cancer Society, Inc., and National Cancer Institute, U. S. Public Health Service. 961 pages, illustrated. $9.00. Philadelphia and Montreal: J. B. Lippincott Co., 1957.

The conference consisted of a series of symposia and panel discussions on clinical types of cancer, such as, cancers of breast, prostate, uterus, as well as lymphomas and leukemia. These topics were discussed by qualified authorities from the biologic, pathologic, etiologic, and therapeutic angles. The different types of therapy were contrasted and the reasons for failure examined.

As an example, there were 12 papers on the breast covering the different aspects already mentioned. There were 6 prepared discussions interspersed at the proper intervals. Prostatic cancer was handled as a panel discussion between biochemists, pathologists, clinicians, and statisticians, 5 major subjects being discussed in a give and take question and answer period with moderators controlling the panels. Following these 2 sessions, there was a joint symposium on cancer of the breast and of the prostate during which all the varied hormonal therapeutic trials were evaluated.

In the symposium on lymphoma and leukemia it was timely to introduce the new concepts of the chemotherapeutic approach and possible virus etiology. Animal experimentation and case material from human beings received equal attention.

A symposium on chemotherapy made possible a review of the metabolism of cancer cells and the modes of action of the antimetabolic drugs. The mechanisms of resistance to these therapeutic agents and the possibility of selective toxic action on cancer cells were discussed. These studies involved the search for the sites of action of the drugs through their use in tissue culture of cells in vitro. The basic pathways by which cells build up their purine nucleotide metabolism have been partially uncovered by tracer experiments and paper chromatography.

In the symposium on cancer of the lung, a series of 13 papers and 5 prepared discussions covered the subject of treatment from the experimental to the definitive aspects. The effects of tobacco smoking and atmospheric pollutants were explored by pathologists and statisticians. The early diagnosis through exfoliative cytologic studies indicated the advances that have been made by this method. The roentgen screening of patients without symptoms has been helpful in the recognition of otherwise unsuspected pulmonary lesions.

In the discussion of cancer of the head and neck, contrasting radiotherapeutic and surgical treatments constituted the main topics. The role of supervoltage radiation was appraised. More radical surgery, plastic reconstruction, and prostheses were considered.

The symposium on cancer of the female genital tract stressed cytologic diagnosis. Cancer in situ was emphasized as being a precancerous lesion with definite malignant potential although slowly progressive. In young women it was considered even safe to allow pregnancies before proceeding to later eradication of the lesion. No advances have been made in the treatment of ovarian cancer during recent years.

Cancer of the gastrointestinal tract was covered in a series of 16 papers and 2 prepared discussions. There have been no significant advances in the field of gastric, pancreatic, or small intestinal cancers. Radical surgical procedures have been developed to remove primary and secondary liver cancers. Those experiments have indicated that it is possible to get along even though very little liver substance remains. An interesting physiologic study will be possible if a sufficient number of survivors remain. The "second look" operation of Wangensteen has been continued by his group. The procedure is still in the investigative stage, and there seems to be little likelihood that it will become a popular operation.

The newly discovered syndrome of fulminating ulcer diathesis associated with adenomas of the islet alpha cells has been added to the knowledge of pancreatic disorders. Differential diagnosis between carcinomas of the head of the pancreas, carcinomas of the ampulla of Vater, and chronic inflammatory pancreatitis may be made by surgeons experienced in this field of surgery. The importance of making these distinctions is in the better prognosis for the latter two conditions.

The concluding symposium on end results in the treatment of cancer covered 11 important regional areas. This portion of the National Cancer Conference should be of inestimable value to clinicians faced with deciding what therapy to offer their patients. The end results were obtained by requesting information from 70 sources such as, central registries, hospital registries, and specialists. One-half of those approached submitted their results. The data covered the end results in 19 sites or types of neoplastic disease, excluding skin cancer, in 66,087 patients over a 5 year period. This amounted to a 3 per cent sample of the total cancer in the country during a similar time. Tables of end results at the end of this volume make it possible for physicians to appraise the possibilities of therapy for localized regional or distant cases. Comparisons of surgery, radiotherapy, and chemotherapy are available and should be of great help to everyone concerned.

Whereas there have been no startling discoveries in the field of cancer during the last 10 years, a feeling of optimism prevailed at this meeting. There has been a slow but steady progress toward the resolution of the basic problems of growth. The chemical discoveries indicate that the nuclear material, genes, and viruses may all be of the same pattern and what now appear to be wide differences may resolve into similarities.

In the meantime, the clinician must use the best available means at his command to treat patients suffering from cancer. The extension of surgery into difficult areas; the more powerful ionizing radiations; the detoxification of the chemotherapeutic drugs; the weighing of the endocrine factors; and the chance of immunization against cancer are under surveillance now as indicated in these *Proceedings*. During the next 10 years, research in the field of cancer promises to be exciting. —*John J. Morton.*

ALL ASPECTS of Strümpell-Marie disease, and especially the clinical features and modes of treatment, are considered in the book, *Ankylosing Spondylitis*,[8]

[8]ANKYLOSING SPONDYLITIS; CLINICAL CONSIDERATIONS, ROENTGENOLOGY, PATHOLOGIC ANATOMY, TREATMENT. By J. Forestier, M.D., F.A.C.R.(Hon.), F. Jacqueline, M.D., and J. Rotes-Queroi, M.D. Translated by A. U. Desjardins, M.S., M.D., F.A.C.P., F.A.C.R. 374 pages, 145 illustrations. $10.75. Springfield, Ill.: Charles C Thomas, 1956.

translated from the French edition (1951). The authors, who have been interested in this disease for many years, are clinicians, and the book is written primarily for clinicians. Internists, orthopedic surgeons, radiologists, and general practitioners will also find very useful information concerning the aspect of this disease with which they are most concerned.

The numerous statistics are based upon a careful study of hundreds of patients, the authors' own cases, many of which were followed-up for more than 20 years.

Detection of the disease through the early clinical and radiologic symptoms is emphasized. The most important chapter (one-third of the book) deals with every detail of the spinal and paraspinal symptoms. The modes of onset and evolution are treated in another very interesting chapter. Fine histologic sections illustrate the study of the pathologic findings.

The different methods of treatment (orthopedic, surgical, radiologic, and pharmacologic) are discussed according to the authors' own experience. The management of the patients is carefully analyzed in accordance with the severity of the disease and its symptoms. An up-to-date bibliography and many photographs and reproductions of roentgenograms make this book very attractive for anyone interested in this insidious disease. The translation is excellent.

—*Joseph C. Mulier.*

THE BOOK *The Gist of Obstetrics*[9] is the outgrowth of the author's obstetric lecture notes and was stimulated by his thoughts on the futility of taking notes during didactic lectures. It was his desire to supply his students and others with an accurate compendium of the type of obstetrics practiced in Halifax.

The concepts and experiences of the obstetric teachers at Dalhousie University are presented in a clear, concise manner. The writing is informal and conversational, and the side remarks are most entertaining. These comments are not only laugh-evoking but also thought-provoking and are most efficient in emphasizing the author's important points.

The author's strong feelings about natural childbirth as practiced by his group are evident throughout the entire book. The sections on the pelvis and management of labor are clear and informative. They are exceedingly well illustrated with excellent simple line drawings which add greatly to the clarity of the text. The chapter on medical and surgical complications of pregnancy is too brief since it brushes over these most important problems superficially. On the other hand, the sections concerning intrapartum and postpartum complications are direct, concise, and thorough.

Though many would disagree with some of the statements which seem dogmatic at times, it is not claimed "that it is the best obstetrics, but only what we feel is for us the best." Though it is written primarily for medical students and general practitioners, the context and the style are such that it is recommended to all interested in the practice and the teaching of obstetrics. —*Albert B. Gerbie.*

[9]THE GIST OF OBSTETRICS. By H. B. Atlee, M.D., F.R.C.S. Illustrated by Garth Vaughan, M.D. 327 pages, 88 illustrations. $6.00. Springfield, Ill.: Charles C Thomas, 1957.

THE ANSWER to a long felt need for information on certain phases of the subject of bone tumors can be found in the book entitled *Bone Tumors*.[10] In form, it is an atlas that gives in graphic terms the incidence of the various types of bone tumors including a brief description of their symptoms, physical findings, and roentgenographic features with particular emphasis on the gross and pathologic picture. Treatment and prognosis are mentioned but not in great detail. The quality of the illustrations, both the x-ray reproductions and the photomicrographs, is excellent.

The section on the histopathology of chondrosarcoma is particularly well presented and corroborates the reviewer's opinion concerning the difficulty of microscopic interpretation of cartilage tumors.

It is interesting to note that the author has subdivided osteogenic sarcoma as follows: osteoblastic, chondroblastic, and fibroblastic sarcoma. This is a concept which is rapidly gaining ground both in this country and abroad and will probably soon be generally accepted.

While making use of the vast material available at the Mayo Clinic, Dahlin has succeeded in streamlining it to the extent that all extraneous matter has been eliminated.

This book affords obvious advantages to the general surgeon, the orthopedist, the radiologist, and the pathologist for it places at their disposal, in readily accessible form, much information about all forms of bone neoplasms. —*Bradley L. Coley.*

THE BOOK ENTITLED *Fluid Balance Handbook for Practitioners*[11] is composed of 7 parts containing 33 chapters, 28 tables, 27 figures, and 8 plates.

The first part supplies "Foundation Facts," the second "Clinical Diagnosis," the third "Therapy; Changes in Properties of Extracellular Fluid," the fourth "Therapy: Changes in Position of Extracellular Fluid" (when fluid shifts occur), the fifth and sixth parts "Therapy," and the seventh part, case histories with clinical application of theory previously presented.

All data are clearly and simply presented without oversimplification and it is always practical. The references are complete and accurate. The page trim (6 by 9 inches), the type page (26 by 43 picas), the type face, text paper, and quality of cover could be duplicated advantageously by many other publishers.

Most important of all the rationale for better and more intelligent patient care in the presence of fluid imbalance is presented, thus achieving the author's goal. This reviewer sincerely hopes that "the chief desire of the authors that this primer will orient the reader with respect to the clinical disturbances of the body fluids and will stimulate him to the intensive study required for practical mastery," will also be achieved.

Recent personal experience with internes, residents, and senior medical students has taught me that refer-

[10]BONE TUMORS; GENERAL ASPECTS AND AN ANALYSIS OF 2,276 CASES. By David C. Dahlin, M.D. 224 pages, illustrated. $11.50. Springfield, Ill.: Charles C Thomas, 1957.

[11]FLUID BALANCE HANDBOOK FOR PRACTITIONERS. By William D. Snively, Jr., M.D., and Michael J. Sweeney, M.D. Illustrations by Kathleen Calhoun. 326 pages, 27 illustrations. $6.75. Springfield, Ill.: Charles C Thomas, 1956.

ence to this text will help this group, as well as older practitioners, to achieve better patient care.

—*Samuel J. Fogelson.*

THE SECOND EDITION of the text, *The Clinical Management of Varicose Veins*,[12] undoubtedly will be as well received as the first, since it remains a very practical handbook covering the general problem of lower extremity varicosis. It contains very valuable and precise background information as well as specific therapeutic measures as practiced by the author. The illustrations and photographs are of excellent quality and are well balanced with descriptive material. The latter is written in a clear, precise manner.

After a brief historical reference, the anatomic and pathophysiologic factors involved in the production of varicose veins are duly considered. Appropriate reference is made to the "peripheral venous heart" and its importance in the maintenance of venous return flow. In describing the various sources of venous reflux which go into the production of varicose veins the author makes a logical plea for wider use of more descriptive anatomic diagnoses, pointing out the analogy to the method used in cardiology. Treatment of sclerosis and surgical correction of varicosis are described in a very clear manner. The author agrees with the general trend in holding that stripping should be added to the usual saphenous ligations. Although he states that bilateral simultaneous stripping procedures are well tolerated, this reviewer wonders about the psychologic impact of this upon some patients in connection with their future willingness to undergo other surgical procedures. We believe that one leg thoroughly done is sufficient for the average patient on one day. In the author's desire to simplify the surgical correction no reference is made to the fact that perforator veins exist which do not directly connect with the saphenous trunk, as well reported originally by Sherman, and which in some may be the cause of poststripping recurrence.

Some disagreement can be expressed with the author's use of spinal anesthesia for such procedures as vein ligations accompanied by stripping, especially since local infiltrative anesthesia coupled with a short period of intravenous pentothal sodium has proved to be perfectly adequate. Further, if the surgeon wishes to do both legs at one séance he obviously will be "fighting the clock." Emphasis upon the need for speed in such circumstances is to be condemned. Nothing is gained by this emphasis upon speed, and in inexperienced hands this might well lead to serious hemorrhage from fragile veins at the saphenofemoral junction.

While the postphlebitic syndrome is well covered, some readers may have anticipated a more detailed and critical discussion of this problem. This somewhat controversial subject could have been given more space in the text. Certainly, the indications for superficial femoral and popliteal vein ligations remain an enigma for many practicing surgeons, and by many are thought seldom to be of value.

The fact that no mention is made of varicose veins in pregnancy may be considered a shortcoming of the text. Opinions are now sufficiently well developed in some parts of the country to warrant a few paragraphs on this phase of varicosis in order to guide the interested reader and practitioner.

—*Walter W. Carroll.*

REALIZING THE IMPORTANCE of applied physiology in the progress of modern surgery, the authors have compiled, in one volume *Physiologic Principles of Surgery*,[13] an authoritative, up-to-date review of the current status of various physiologic problems encountered in the fields of surgery. Forty-eight collaborators have assisted them. Lengthy historical introductions have been avoided and, for the most part, citations of the literature have been kept to a minimum of the most important references.

The authors are to be commended for their ability to condense the essential current interpretations of the physiologic problems encountered into such a few pages. One must appreciate that entire books have been devoted to the subject covered in many of the individual chapters of the text. To gather all of this information between two covers has been a monumental task.

Chapters 1, 2, and 3 are concerned with the metabolic and physiologic changes associated with injuries and the treatment of infections. Chapter 4 is devoted to the transplantation of tissues with particular reference to those that are now practical. Chapter 5, on hemorrhage and shock, reviews the consequences of circulating blood volume reduction and the indications for replacement therapy. Chapters 7, 8, and 9 summarize the current concepts of body fluid and electrolyte balance; nutritional requirements from the standpoint of foodstuffs and vitamins; and the significance of plasma proteins in surgical practice. Chapter 10 is concerned with the surgery of the newborn with particular reference to the cardiovascular, respiratory, gastrointestinal, and urinary systems of infants. Chapter 11 is a generalization of the factors involved in the production and interpretation of pain with some good, common-sense recommendations for the treatment of pain. Chapter 12, on anesthesia, is an excellent review of the physiologic effects of general anesthesia on various organs and body tissues. There is an adequate section on regional anesthesia but hypothermia, as an anesthetic agent, is given very little attention. Chapter 13 presents a very concise and useful summary of the embryology, pathology, physiology, clinical characteristics, and laboratory aids in the diagnosis of the more common congenital heart lesions. The principles and basic measurements of cardiac catheterization are discussed. This is followed by a short chapter on acquired cardiac lesions. Chapters 15 and 16 interpret the current basis for surgical treatment of hypertension, the peripheral arterial-vascular disorders, and the effects of sympathectomy. Chapter 17 reviews the normal and pathologic physiology of the venous system and the surgical physiology of the lymphatic system. Chapter 18 is an excellent review of

[12]THE CLINICAL MANAGEMENT OF VARICOSE VEINS. By David Woolfolk Barrow, M.D. With a foreword by Arthur W. Allen, M.D. 2nd rev. enl. ed. 169 pages, 70 illustrations. $6.00. New York: Paul B. Hoeber, Inc., 1957.

[13]PHYSIOLOGIC PRINCIPLES OF SURGERY. By Leo M. Zimmerman, M.D., and Rachmiel Levine, M.D. 988 pages, illustrated. $15.00. Philadelphia and London: W. B. Saunders Co., 1957.

the physiology of normal and abnormal respiratory conditions and on the applications of pulmonary function studies to thoracic surgery. The next chapters cover the physiology of normal and abnormal conditions of the gastrointestinal tract and associated organs. Chapter 25 reviews the blood and the blood-forming organs. Chapters 26 through 29 are concerned with the physiologic problems encountered in surgery of the thyroid, parathyroid, adrenals, and the islands of Langerhans. Chapters 30 and 31 review the kidneys and lower urinary tract and are followed by 2 chapters on the male and female genital tracts and 1 on the breast with particular reference to the biochemistry and general physiology of the endocrine secretions as they affect the breast. Chapter 35 is devoted to the physical properties of the locomotor system of muscles, tendons, and bones; the mechanisms of joint and muscle action; and body balance and equilibrium. The final chapter is a short review of the physiology of the central nervous system.

The illustrations are somewhat sparse and, for the most part, consist of black and white line drawings and excellent diagrammatic charts. No attempt has been made to discuss surgical techniques. The book is primarily one of physiology. For the surgical resident and candidate for American Board certification, its value is obvious. I would recommend it especially to the practicing surgeon who is familiar with but has forgotten or does not fully comprehend the physiology of injury, tissue transplantation, steroids, and the functioning of various body systems.

—*Edward W. Gibbs.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

NURSING CARE OF THE SURGICAL PATIENT. 6th ed. By John Pettit West, M.D., Manelva Wylie Keller, B.S., R.N., and Elizabeth H. Harmon, M.A., R.N. 669 pages, illustrated. $5.75. New York: The Macmillan Co., 1957.

SURGERY OF HEAD AND NECK TUMORS. By Hayes Martin, M.D. 430 pages, illustrated. $18.50. New York: Paul B. Hoeber, Inc., 1957

ARTERIOESCLEROSIS PERIFERICA: EXPLORACIÓN, DIAGNÓSTICO Y TRATAMIENTO DE LA OCLUSIÓN ARTERIAL LENTA. By Manuel Casanueva del C. 322 pages, illustrated. Santiago de Chile: Central de Publicaciones, 1956.

INHALATION ANALGESIA IN CHILDBIRTH. By E. H. Seward, M.A., D.M., and R. Bryce-Smith, M.A., D.M. 58 pages, illustrated. $1.50. Springfield, Ill.: Charles C Thomas, 1957.

STUDIES ON FERTILITY. Edited by R. G. Harrison, M.A., D.M. Vol. VIII of the Proceedings of the Society for the Study of Fertility. 138 pages, illustrated. $5.00. Springfield, Ill.: Charles C Thomas, 1957.

LUMBAR PUNCTURE AND SPINAL ANALGESIA. By Sir Robert Macintosh, M.D., D.M., F.R.C.S. 2nd ed. 142 pages, illustrated. $6.00. Baltimore: Williams & Wilkins Co., 1957.

THE COLLECTED PAPERS OF HUGH TRUMBLE. Edited by Leonard Cox, M.D., R. S. Lawson, F.R.C.S., and T. E. Lowe, M.D. 302 pages, illustrated. Victoria, Australia: Melbourne University Press, 1957.

A PRACTICAL HANDBOOK OF MIDWIFERY AND GYNAECOLOGY; FOR STUDENTS AND PRACTITIONERS. By W. F. T. Haultain, O.B.E., and Clifford Kennedy, M.B. 5th ed. 410 pages, illustrated. $7.00. Edinburgh and London: E. & S. Livingstone Ltd., 1957.

IMMUNOPATHOLOGIE IN KLINIK UND FORSCHUNG; UND DAS PROBLEM DER AUTOANTIKOERPER. Edited by P. Miescher and K. O. Vorlaender and others. 601 pages, 171 illustrations. $16.45. Stuttgart: Georg Thieme, 1957.

ANATOMIE MÉDICO-CHIRURGICALE; ANATOMIE DES FORMES EXTÉRIEURES ET ANATOMIE DES RÉGIONS. Vol. XI. By Prof. Philippe Bellocq. 154 pages, illustrated. 2000 fr. Paris: Masson et Cie, 1957.

BASES, PRINCIPES ET PROCÉDÉS TECHNIQUES DE LA CHIRURGIE. By Paul Orsoni. 276 pages, illustrated. 2.400 fr. Paris: Masson et Cie, 1957.

CHIRURGIE À COEUR OUVERT. By Prof. Ch. Dubost and Ph. Blondeau. 320 pages, illustrated. 3.000 fr. Paris: Masson et Cie, 1957.

MEDICINE AND THE NAVY 1200–1900. By J. J. Keevil Vol. I—1200–1649. 255 pages, illustrated. $8.50. Edinburgh and London: E. & S. Livingstone Ltd., Baltimore: Williams & Wilkins Co., 1957.

THE LIFE, WORK AND TIMES OF CHARLES TURNER THACKRAH, SURGEON AND APOTHECARY OF LEEDS (1795–1833). By A. Meiklejohn. 238 pages, illustrated. $6.00. Edinburgh and London: E. & S. Livingstone Ltd.; Baltimore: Williams & Wilkins Co., 1957.

TEXT-BOOK OF ORTHOPAEDIC MEDICINE; DIAGNOSIS OF SOFT TISSUE LESIONS. Vol. I. 3rd ed. By James Cyriax, M.D., M.R.C.P. 711 pages, illustrated. $10.50. New York: Paul B. Hoeber Inc., 1957.

THE ANATOMY OF CONGENITAL PULMONARY STENOSIS. By Sir Russell Brock, F.R.C.S., F.A.C.S. 114 pages, illustrated. $7.50. New York: Paul B. Hoeber, Inc., 1957.

THE HEALING OF WOUNDS; A SYMPOSIUM ON RECENT TRENDS AND STUDIES. Edited by Martin B. Williamson, Ph.D. 202 pages, illustrated. $7.00. New York: McGraw-Hill Book Co., Inc., 1957.

AIDS TO DIAGNOSIS AND TREATMENT OF DISEASES OF CHILDREN. By F. M. B. Allen, M.D., F.R.C.P. (Lond.). 10th ed. 302 pages, not illustrated. $3.00. London: Baillière, Tindall & Cox, 1957.

TRANSACTIONS OF THE INTERNATIONAL SOCIETY OF PLASTIC SURGEONS. First Congress (Stockholm and Uppsala 1955). Edited by Tord Skoog, M.D., with the help of others. 568 pages, illustrated. $20.00. Baltimore: The Williams & Wilkins Co., 1957.

SURGERY IN WORLD WAR II. OPHTHALMOLOGY AND OTOLARYNGOLOGY. Editor in chief, Col. John Boyd Coates, Jr., M.C. Editor for Ophthalmology, M. Elliott Randolph, M.D. Editor for Otolaryngology, Norton Canfield, M.D., Associate Editor, Elizabeth M. McFetridge, M.A. 605 pages, illustrated. Washington, D. C.: Office of the Surgeon General, 1957.